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

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

Abstract—Obesity is becoming a global epidemic in both children and adults, and it is associated with numerous co-morbidities such as cardiovascular diseases (CVD), type 2 diabetes, hypertension, certain cancers, and sleep apnea/sleep-disordered breathing. In fact, is an independent risk factor for CVD and CVD risks have been also documented in obese children, and is associated with reduced life expectancy. A variety of adaptations/alterations in cardiac structure and function occur in the individual as adipose tissue accumulates in excess amount. As a whole, overweight/obesity predispose or is associated with numerous cardiac complications such as coronary heart disease, heart failure, and sudden death through its impact on the cardiovascular system. (Arterioscler Thromb Vasc Biol. 2006; 26:968-976.)

Key Words: congestive heart failure ■ myocardial biology, structure

Obesity as a Metabolic/Genetic Cardiovascular Disease Risk Factor

An explosive increase in the number of people with the Metabolic Syndrome (MetS) has taken place all around the globe. Several definitions of the MetS have been published and this issue has been reviewed lately.11 The MetS is associated with an increased risk of both diabetes12 and cardiovascular disease (CVD).13–16 Abdominal obesity is a risk factor for CVD worldwide,17,18 but the estimated years of life lost attributable to obesity differs among races and gender.19 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.20,21 There are presently more than 41 sites on the genome that have been identified as possible links to the development of obesity in a favorable environment.22

Beside an altered metabolic profile, a variety of adaptations/alterations in cardiac structure and function occur in the individual as adipose tissue accumulates in excess amount,23 even in the absence of co-morbidities. As a whole, overweight/obesity predispose or is associated with numerous cardiac complications such as coronary heart disease (CHD), heart failure, and sudden death through its impact on the cardiovascular system.

Cardiomyopathy of Obesity (Adipositas Cordis)

Initially, the fatty heart is probably not an infiltrative process but most likely a metaplasic phenomenon.24 Cords of cells can gradually accumulate fat between muscle fibers and/or result in myocyte degeneration resulting in cardiac dysfunction.10 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.25 An alternative explanation explaining the pathophysiology of the cardiomyopathy of obesity is the lipotoxicity of the myocardium induced by free fatty acids, which can cause apoptosis of lipid-laden cells such as cardiomyocytes.26

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

**Assessment of Obese Individuals and Co-Morbidities**

The physical examination and ECG often underestimate the presence and extent of cardiac dysfunction in obese patients.

**ECG**

Like physical evaluation, the ECG is influenced by morphological changes induced by obesity such as (1) displacement of the heart by an elevated diaphragm, (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.

There are several changes in the ECG with increasing obesity (Table 2). Multiple ECG criteria for LVH are present more regularly in morbid obesity compared with lean individuals but less frequently than might be expected based on the high prevalence of echocardiographic LVH in such patients. It was proposed that for men, LVH is present by QRS voltage alone when the appearance of the R wave in lead AVL and the S wave in lead V3 are >35 mm. For women, the same criteria were set at >25 mm. Thus, Sokolow-Lyon voltage should be replaced by the Cornell voltage criteria, which seems to be less influenced by the presence of obesity.

The impact of weight loss in obese patients on the QRS voltage is not consistent. With weight loss, a decreased amount of fat mass may counterbalance a true decrease in left ventricular mass.

**Echocardiography**

In times past, obesity-induced cardiac abnormalities were found only post-mortem. Differentiation between subepicardial adipose tissue and pericardial effusion is often difficult in obese patients, and epicardial adipose tissue is known to be a common cause of false-positive effusion. The increased intravascular volume in obesity may mask the Doppler-derived abnormalities of diastolic filling. Indexing left ventricular mass using height or height may be more appropriate than normalization for body surface area or even for height in obese patients, but using lean body mass may be even more suitable. Indeed, stroke volume and cardiac output are more strongly related to fat free mass than other variables in both normal weight and overweight individuals.

**Venous Insufficiency, Venous Thrombosis, and Pulmonary Embolus**

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. 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 attributable to venous valvular incompetence. The risk of the severe and sustained lower extremity venous stasis disease in severe obesity is pretribial ulceration and cellulitis. In the absence of right heart failure, surgically-induced weight loss is effective in correcting the venous stasis disease in the majority of patients. The incidence of venous thromboembolism (VTE) is increased in obesity. Obesity has also been associated with an increased risk of pulmonary embolism in women, but this is less clear for men.

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

<table>
<thead>
<tr>
<th>Disease Risk* Relative to Normal Weight and Waist Circumference</th>
<th>BMI (kg/m²)</th>
<th>Men, ≤102 cm; Women, ≤88 cm</th>
<th>Men, &gt;102 cm; Women, &gt;88 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5–24.9</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0–29.9</td>
<td>Increased</td>
<td>High</td>
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<tr>
<td>Obesity, class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>30.0–34.9</td>
<td>High</td>
<td>Very high</td>
</tr>
<tr>
<td>II</td>
<td>35.0–39.9</td>
<td>Very High</td>
<td>Very High</td>
</tr>
<tr>
<td>III (extreme obesity)</td>
<td>≥40</td>
<td>Extremely High</td>
<td>Extremely High</td>
</tr>
</tbody>
</table>


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**TABLE 2. ECG Changes That May Occur in Obese Individuals**

<p>| | | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>↑ Heart rate</td>
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<tr>
<td>↑ PR interval</td>
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<td></td>
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<tr>
<td>↑ QRS interval</td>
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<tr>
<td>↑ or ↓ QRS voltage</td>
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<td></td>
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<tr>
<td>↑ QTc interval</td>
<td></td>
<td></td>
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<tr>
<td>↑ QT dispersion</td>
<td></td>
<td></td>
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<tr>
<td>↑ SAECG (late potentials)</td>
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<td></td>
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<tr>
<td>ST-T abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST depression</td>
<td></td>
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<tr>
<td>Left axis deviation</td>
<td></td>
<td></td>
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<tr>
<td>Flattening of the T wave (inferolateral leads)</td>
<td></td>
<td></td>
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<tr>
<td>Left atrial abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>False positive criteria for inferior myocardial infarction</td>
<td></td>
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</tbody>
</table>
Hypertension
The majority of patients with high blood pressure are overweight, and hypertension is more frequent in obese subjects. A 10 kg higher body weight is associated with a 3.0 mm Hg higher systolic and 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. Results from NHANES III reported more specific estimates for the prevalence of high blood pressure per age and BMI group. This increase in blood pressure is greatest when the obesity is of abdominal distribution. Factors to be considered in linking obesity to an increase in blood pressure include: (1) direct effects of obesity on hemodynamics: increase in blood volume, stroke volume, and cardiac output; and (2) mechanisms linking obesity and an increase in peripheral vascular resistance: endothelial dysfunction, insulin resistance, sympathetic nervous system, substances released from adipocytes (interleukin [IL]-6, tumor necrosis factor [TNF]-α, etc.), and sleep apnea. 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 diastolic 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. Of note, after the weight loss has ceased, the persistent effect of weight loss on blood pressure may not always be encountered.

Sleep Apnea
The prevalence of sleep-disordered breathing and sleep disturbances rises dramatically in obese subjects, and obesity is by far the most important modifiable risk factor for sleep-disordered breathing. 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 classical cause of alveolar hypoventilation. Numerous treatments are available for sleep apnea but weight loss in obese patients should always be advocated.

Stroke
Numerous studies have reported an association between BMI and waist-to-hip ratio and stroke. 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. The increase of stroke in obesity may be predicted by the prothrombotic/proinflammatory state that so often accompanies excessive adipose tissue accumulation.

Coronary Artery Disease
Examination of arteries post-mortem 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. Black subjects had more extensive fatty streaks than white subjects in all arterial segments examined, and men did have more extensive raised lesions in the RCA than women. Of note, it was reported that the maximal density of macrophages/mm² in the lesions was associated with visceral obesity. Raised lesions in coronary arteries observed in young women lagged behind by 10 to 20 years to those seen in young men. The preferential deposition of fat centrally after menopause may in part explain why the risk for CHD events increases later in women. Prospective studies that have reported follow-up data over more than two 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. In contrast, in patients with known CVD or after acute myocardial infarction, overall obesity as assessed by BMI is inversely related to mortality, whereas 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 25% compared with patients who were not abdominally obese.

Coronary Artery Disease Revascularization Procedure in Obesity
Today, obesity is encountered more frequently in the catheterization laboratory where obese patients are younger with more co-morbidities, but showing more single-vessel disease at baseline. Abnormal glucose tolerance may be an important determinant for long-term prognosis after coronary angioplasty, which may be dependent on the features of the MetS. After coronary artery bypass, the components of the insulin resistance syndrome are associated with angiographic progression of atherosclerosis in non-grafted coronary arteries. Therefore, abnormalities of glucose metabolism with features of the MetS could modulate the extent of atherosclerosis within the coronary artery tree and mediate acute coronary syndrome events. In contrast to frequent beliefs, obesity is not associated with increased mortality or postoperative cerebrovascular accidents after CABG. However, an increased incidence of sternal and superficial wound infection, saphenous vein harvest site infection, and atrial dysrhythmias was seen. On the other hand, severely obese patients (BMI >35 kg/m²) are more likely to have prolonged mechanical ventilation and longer post-operative stay.

Congestive Heart Failure
Elevated BMI predisposes to congestive heart failure (CHF) by promoting hypertension, diabetes, and CHD. It is estimated that there is an increase in the risk of CHF of 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.\textsuperscript{131} In contrast, once the patient presents with CHF, the presence of obesity may not adversely affect the patient’s outcome.\textsuperscript{114–116} Indeed, among patients with CHF, subjects with higher BMI are at decreased risk for death and hospitalization compared with patients with a “healthy” BMI.\textsuperscript{114,116–120} On the contrary, preoperative obesity (>140% ideal body weight) may increase morbidity and mortality after heart transplantation.\textsuperscript{121}

### Arrhythmias

Weight-stable obese subjects have an increased risk of arrhythmias and sudden death, even in the absence of cardiac dysfunction,\textsuperscript{122,123} and the risk of sudden cardiac death with increasing weight is seen in both genders.\textsuperscript{92} In the Framingham study, the annual sudden cardiac mortality rate in obese men and women was estimated to be ~40 times higher than the rate of unexplained cardiac arrest in a matched non-obese population.\textsuperscript{92,122} 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.\textsuperscript{124}

Prolonged QT\textsubscript{c} interval was observed in ~30% of subjects with impaired glucose tolerance,\textsuperscript{125} and there is a positive association between BMI and QT\textsubscript{c}.\textsuperscript{126} When visceral obesity or insulin levels increase, sympathovagal balance may be the best explanation for changes in QT\textsubscript{c}.\textsuperscript{127} The clinical significance of obesity-associated QT prolongation and the mechanisms involved remain speculative. High glucose concentrations may promote increased vasomotor tone and ventricular instability by reducing nitric oxide availability.\textsuperscript{128,129} Moreover, because extremely obese patients often have a dilated cardiomyopathy, fatal arrhythmias may be the most frequent cause of death.\textsuperscript{123,130} Obesity and 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.\textsuperscript{131} It was demonstrated that a 10% weight loss in severely obese patients is associated with significant improvement in autonomic nervous system cardiac modulation.\textsuperscript{132}

### 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.\textsuperscript{9,133} 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 American Heart Association.\textsuperscript{9} 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.\textsuperscript{134,135} Table 3 enumerates the beneficial impacts of weight loss on the cardiovascular system. Sympathetic mechanisms have been implicated in the development of LHV,\textsuperscript{136} and weight reduction in obese subjects reduces the indices of sympathetic activity. The renin–angiotensin system may also be involved in the pathogenesis of LHV, and weight reduction may decrease plasma renin activity and aldosterone levels.\textsuperscript{137} The improvement in hyperinsulinemia may also be related to the reduction in left ventricular mass in hypertensive obese subjects.\textsuperscript{138} A reduction in angiotensin-converting enzyme activity after weight reduction could also be important.\textsuperscript{139}

### Risks of Weight Loss

Weight loss through different modalities, ie, starvation,\textsuperscript{40,140} liquid protein diets,\textsuperscript{38,39} very low calorie diets, and even obesity surgery,\textsuperscript{141} has been associated with prolongation of the QT interval. Most importantly, liquid protein diets that have been associated with potentially life-threatening arrhythmias were only suspected after a 24-hour Holter recording.\textsuperscript{142} 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 after reports of cardiac-valve disorders.\textsuperscript{143} There was also an increased risk of primary pulmonary hypertension documented.\textsuperscript{144–147}

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 co-morbidities.\textsuperscript{148,149} Sibutramine hydrochloride, a centrally acting drug,\textsuperscript{150} which is approved for long-term use, has not been associated with valve abnormalities.\textsuperscript{151,152} However, increases in blood pressure and heart rate may occur

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**TABLE 3. Benefits of Weight Reduction on the Cardiovascular System**

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Impact</th>
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<tr>
<td>↓ blood volume</td>
<td></td>
</tr>
<tr>
<td>↓ stroke volume</td>
<td></td>
</tr>
<tr>
<td>↓ cardiac output</td>
<td></td>
</tr>
<tr>
<td>↓ pulmonary capillary wedge pressure</td>
<td></td>
</tr>
<tr>
<td>↓ left ventricular mass</td>
<td></td>
</tr>
<tr>
<td>Improvement of left ventricular diastolic dysfunction</td>
<td></td>
</tr>
<tr>
<td>Improvement of left ventricular systolic dysfunction</td>
<td></td>
</tr>
<tr>
<td>↓ Resting oxygen consumption</td>
<td></td>
</tr>
<tr>
<td>↓ Systemic arterial pressure</td>
<td></td>
</tr>
<tr>
<td>↓ Filling pressures of the right and the left side of</td>
<td></td>
</tr>
<tr>
<td>the heart</td>
<td></td>
</tr>
<tr>
<td>↓ or no change in systemic arterial resistance</td>
<td></td>
</tr>
<tr>
<td>↓ resting heart rate</td>
<td></td>
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<tr>
<td>↓ QT, interval</td>
<td></td>
</tr>
<tr>
<td>↑ HRV</td>
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</table>

HRV indicates heart rate variability.
with the use of this drug, and like phentermine, sibutramine should not be used in patients with untreated hypertension, CHD, CHF, arrhythmias, or stroke. The impacts of the endocannabinoid receptor antagonists in the treatment of obesity on heart structure and function are not known.

**Obesity and the Future of Health Care Services**

Health service usage and medical costs associated with obesity and related diseases have and will increase dramatically. Waist circumference may be a better predictor of health care costs than the widely used BMI. Increased physical activity early in life may become the cost effective option, CHD, CHF, arrhythmias, or stroke. The impacts of the endocannabinoid receptor antagonists in the treatment of obesity on heart structure and function are not known.

Conclusions

Obesity is a chronic metabolic disorder associated with CVD and increased morbidity and mortality. 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 dilatation 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 dilatation, 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. There is also an increased risk of sudden cardiac death in obesity.

Hopefully, within the next decade, new information may be provided that weight reduction is beneficial for hard CVD outcomes, ie, CHD events, CHD death, CHF, stroke, and total mortality. Until then, the clinical approach must hope that such a favorable result will ensue. 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.

**References**


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