Cardiac Energy Metabolism in Obesity

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Abstract—Obesity results in marked alterations in cardiac energy metabolism, with a prominent effect being an increase in fatty acid uptake and oxidation by the heart. Obesity also results in dramatic changes in the release of adipokines, such as leptin and adiponectin, both of which have emerged as important regulators of cardiac energy metabolism. The link among obesity, cardiovascular disease, lipid metabolism, and adipokine signaling is complex and not well understood. However, optimizing cardiac energy metabolism in obese subjects may be one approach to preventing and treating cardiac dysfunction that can develop in this population. This review discusses what is presently known about the effects of obesity and the impact adipokines have on cardiac energy metabolism and insulin signaling. The clinical implications of obesity and energy metabolism on cardiac disease are also discussed. (Circ Res. 2007;101:335-347.)

Key Words: fatty acid oxidation ■ adiponectin ■ leptin ■ malonyl–coenzyme A ■ PPARα ■ glycolysis

It is well established that obesity greatly increases the risk for coronary artery disease1 and heart failure.2 The recent epidemic in obesity is likely a major driving force for the continued prevalence of ischemic heart disease in developed countries and for the increase in cardiovascular related death in developing countries. Although obesity can contribute to cardiac dysfunction, the mechanistic links are not well understood. Recent studies suggest that the alterations in cardiac fatty acid metabolism that occur in obesity may play a causal role in the development of obesity-related cardiomyopathies because of both altered cardiac metabolic phenotype and elevated circulating free fatty acids and triacylglycerol levels, which can lead to cardiac lipid accumulation and excessive fatty acid utilization.

In reviewing the relationship between obesity and cardiac energy metabolism, it is important to recognize that “obesity” does not occur in isolation from other metabolic disorders. Obesity is defined as an excess amount of body fat in relation to lean mass, such that adverse health consequences may occur, and overweight is defined as an increase in body weight in relation to height. Although obesity is a risk factor for developing insulin resistance or diabetes, not every obese patient is necessarily insulin resistant or diabetic. In addition, there is a group of patients who are of normal weight but are metabolically obese, ie, they have the metabolic hallmarks of obesity.3 The metabolic syndrome is also associated with obesity, although lipid disorders, hypertension, and insulin resistance, which occur in the metabolic syndrome, do not necessarily accompany obesity. However, obesity is often accompanied by these pathologies; thus one needs to keep in mind that changes in cardiac function and metabolism in obesity may not be occurring in isolation. It is also clear that
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The heart has a very high energy demand, which is met almost entirely by the mitochondrial oxidation of fatty acids and carbohydrates (glucose and lactate) (Figure 1) (reviewed elsewhere24). Fatty acids are the major fuel, with its use depending both on the supply of fatty acids to the heart and cellular control of fatty acid uptake and metabolism (Figure 1). Intracellular control of fatty acid oxidation also occurs at the level of mitochondrial uptake of fatty acids by carnitine palmitoyltransferase (CPT)1, which transfers the fatty acid moiety from acyl–coenzyme A (CoA) to long chain acylcarnitine, which is then transported into the mitochondria.25,26 If CPT1 activity is decreased, long-chain acyl-CoA can be redirected toward complex lipid synthesis, including triacylglycerol, diacylglycerol, phospholipids, sphingolipids, and ceramides. Malonyl-CoA is a potent inhibitor of CPT1 and an important determinant of fatty acid oxidation in the heart. Myocardial malonyl-CoA is primarily produced by acetyl-CoA carboxylase (ACC) and is degraded by malonyl-CoA decarboxylase.24,27–29 AMP-activated protein kinase (AMPK) plays an important role in regulation of malonyl-CoA content by phosphorylating and inhibiting ACC, leading to an increase in fatty acid oxidation.30,31

This increase in fatty acid oxidation has an important suppressive effect on carbohydrate oxidation in the heart through inhibition of glycolysis in the cytosol and pyruvate dehydrogenase in the mitochondria (Figure 1).

The effects of obesity on substrate selection in the heart have not been extensively investigated. Some of the impediments to understanding myocardial metabolism in obesity is: (1) the difficulty in obtaining data from patients, (2) the expense and poor characterization of large animal models of obesity, and (3) the limitations of existing rodent models. The most relevant rodent model of the human pathophysiology is the diet-induced obesity models, whereby a high percentage of caloric intake is from fat, resulting in weight gain, increase in fat mass, and insulin resistance.35,36 Several rat models of obesity have also been developed to mimic the human condition, including the Zucker fatty rat,37 the JLR/LA rat,38 and the SHROB “Koletsky” rat39; several mouse models have

obesity results in alterations in both the renin–angiotensin systems and adrenergic pathways.4–6 These alterations contribute to obesity-related hypertension, which in turn can contribute to the development of hypertrophy and cardiomyopathies. Obesity is also an important contributor to cardiac hypertrophy and diastolic dysfunction.7 Because of space restriction, this review focuses on the contribution of energy metabolic changes to cardiomyopathy development in obesity.

Lipid accumulation within the myocardium, or cardiac lipotoxicity, is attributable to an imbalance between fatty acid uptake and oxidation.8 Although high circulating levels of fatty acids are likely an important contributor to fatty acid accumulation,9 it is less clear whether alterations in cardiac fatty acid oxidation rates contribute to this fatty acid accumulation. In other tissues, such as skeletal muscle and liver, low fatty acid oxidation rates have been implicated in the development of insulin resistance and lipotoxicity.10–16 However, recent studies in mice,17–20 rats,21 and humans22,23 do not support the concept that low fatty acid oxidation contributes to accumulation of toxic lipids in the heart and have shown that cardiac fatty acid oxidation rates are actually elevated in obesity, insulin resistance, and type 2 diabetes. Because high rates of fatty acid oxidation result in a concomitant direct inhibition in glucose oxidation,17–20 and a decrease in insulin-stimulated glucose oxidation, we propose that high rates of fatty acid oxidation in the setting of obesity contributes to insulin resistance because of the direct inhibition of glucose metabolism. Obesity also alters the secretion of the recently discovered adipokine hormones (eg, leptin and adiponectin), which affects cardiac fatty acid metabolism and multiple signaling pathways in the heart.

This review discusses what is presently known about the effects of obesity on cardiac energy metabolism, gene expression, and cardiac function. The impact of adipokines on cardiac energy metabolism, signaling pathways, and the ability of the heart to adapt to acute and chronic stress is addressed. Lastly, the clinical implications of the influence of obesity on energy metabolism and heart disease are discussed.
also been developed, including the db/db (truncated leptin receptor) \(^40\) and ob/ob (defective leptin) mouse. \(^40,41\) Animal models involving targeted gene overexpression or deletion that are used to study the systemic effects of obesity have also been developed. \(^42\) There are also several mouse models of altered cardiac lipid metabolism that result in either excessive lipid uptake or impaired lipid oxidation, which result in cardiac lipotoxicity in the absence of obesity. \(^8,43,44,46\) Although it is difficult to compare data from these models because of the divergent causes of the obesity and/or cardiac pathology and the confounding effects of hypertension and hyperglycemia in some strains, these models have provided key insights to potential mechanisms of cardiac dysfunction in obese patients.

Both human studies and the use of these experimental models have shown an important contributing factor to altered cardiac energy substrate selection in obesity are elevated circulating fatty acids and triacylglycerol levels. Several clinical studies have observed that circulating fatty acids are elevated in obese patients compared with their lean counterparts, with the effect being particularly prominent in females. \(^47\) In addition, not only do plasma triglycerides increase in obesity but myocardial triglyceride content also increases progressively with body mass index. \(^48\) An increase in circulating fatty acids and triglycerides also occurs in animals models of obesity, including the fatty Zucker rat. \(^49–51\) The ob/ob and db/db mouse, \(^51,52\) and mouse models of diet induce obesity, \(^35,36,53\) Recent clinical \(^22\) and experimental studies \(^18,20,52,54–57\) have found that fatty acid oxidation is increased in obesity and insulin resistance. Elegant human studies using positron emission tomography and \(^14\)C-palmitate imaging showed that obese women and type 2 diabetic patients have an increased uptake and oxidation of fatty acids. \(^52,53\) Studies using isolated working hearts from obese insulin-resistant ob/ob and db/db mice found elevated fatty acid oxidation compared with normal control mice. \(^18,20,54,55\) The increase in fatty acid oxidation is paralleled by a decrease in glucose oxidation and glycolysis coupled with a decrease in cardiac mechanical efficiency. In addition, mitochondrial respiration with palmitate as a substrate is relatively preserved on obese mice, whereas oxidation of pyruvate and pyruvate dehydrogenase activity are significantly reduced, which is consistent with the concept that obesity does not impair mitochondrial fat metabolism but rather affects carbohydrate oxidation in a manner similar to diabetes. \(^57\) These recent studies in mice parallel studies in obese insulin-resistant JCR/LA rats, in which an increase in fatty acid oxidation is observed. \(^56\) We have also shown that in isolated hearts from mice with diet-induced obesity and insulin resistance, the contribution of fatty acids to overall energy production is increased, resulting in glucose intolerance and insulin resistance (Table). On the other hand, fatty acid oxidation is unchanged or reduced in perfused hearts from obese Zucker rats. \(^59\) Taken together, the majority of published studies suggest that cardiac fatty acid oxidation rates are increased, not decreased, in obesity and insulin resistance, suggesting that impaired fatty acid oxidation does not contribute to the lipid accumulation seen under these conditions.

### Fatty Acids As Regulators of Metabolic Phenotype

Fatty acids in the heart are also endogenous ligands for peroxisome proliferator-activated receptors (PPARs) and regulate the expression of genes encoding key proteins controlling myocardial fatty acid uptake and metabolism. \(^58,59\) This includes PPAR\(\alpha\), which regulates the expression of proteins involved in fatty acid uptake and oxidation. \(^59\) PPAR\(\gamma\), which is predominantly expressed in adipose tissue, increases storage of triglycerides in adipose tissue. \(^58\) The activation of both PPAR\(\alpha\) or PPAR\(\gamma\) lowers circulating fatty acid and triacylglycerol levels. \(^60\) PPAR\(\gamma\) can reduce fatty acid levels by promoting a “futile” fatty acid cycle resulting from expression of glycerol kinase. \(^61\) PPAR\(\beta/\delta\) also regulates expression of key proteins involved in myocardial fatty acid metabolism, as evidenced by a dramatic decrease in fatty acid oxidation with cardiac-specific deletion of PPAR\(\beta/\delta\) in mice. \(^62\)

Known PPAR\(\alpha\) target genes include enzymes of peroxisomal and mitochondrial fatty acid \(\beta\)-oxidation (acyl-CoA dehydrogenases, 3-ketoacyl-CoA thiolases, acyl-CoA ox-
Fatty Acid Contribution to Cardiac Pathology

Alterations in fatty acid metabolism can contribute to a number of cardiac pathologies. Patients with inherited defects in mitochondrial fatty acid oxidation frequently develop cardiomyopathy, with LV hypertrophy, LV remodeling, and heart failure associated with cardiac lipid accumulation. A clear link between lipid accumulation and cardiomyopathy was established in several transgenic mouse models in which the rate of lipid uptake or esterification of fatty acids by the heart was increased or the capacity for oxidation of fatty acids was reduced in the mitochondria. Similarly, obese hyperlipidemic Zucker rats develop cardiomyopathy associated with accumulation of intracellular triacylglycerol and ceramide, which can be prevented by lowering plasma triacylglycerol, free fatty acid, and glucose concentrations with a PPARγ agonist.

The clinical significance of these findings in patients without genetic defects in metabolism is unclear. At present, there is no strong evidence that obese individuals with chronically elevated plasma triacylglycerol and/or free fatty acids have elevated cardiac lipid accumulation or lipid-induced cardiac pathology. In a small study, heart failure patients with elevated cardiac triacylglycerol content had more severe changes in the mRNA levels of genes that are known to change in severe failure heart (eg, tumor necrosis factor-α or myosin heavy chain-β), however there was no evidence of worse clinical heart failure or ventricular dysfunction in this subgroup. High circulating levels of fatty acids also contribute to the severity of ischemic injury in the heart. The detrimental effects of fatty acids are attributable, in part, to a decrease in glucose oxidation both during and following ischemia secondary to high rates of fatty acid oxidation. In addition, following ischemia, cardiac malonyl-CoA levels decrease, resulting in an increase in CPT1 activity. We have shown that this is attributable to activation of AMPK, which phosphorylates and inhibits ACC, as well as maintained malonyl-CoA decarboxylase activity. In diabetic hearts, high AMPK and malonyl-CoA decarboxylase activity can exacerbate this ischemic injury. The increase in CPT1 activity and the high circulating levels of fatty acids that are seen following ischemia results in fatty acids dominating as a carbon source for residual oxidative metabolism (up to 80% to 90% of the energy requirement). This inhibits pyruvate oxidation and increases lactate production, which generates protons that exchange for other cations, leading to intracellular Ca²⁺ overload. ATP used to reestablish H⁺, Na⁺, and Ca²⁺ homeostasis decreases cardiac efficiency both during and following ischemia.

Experimental and clinical studies have shown that pharmacologically inhibiting fatty acid oxidation and stimulating glucose oxidation has antiischemic effects and can improve recovery of cardiac function and efficiency. A new class of pharmacological agents that inhibit fatty acid oxidation and stimulate glucose oxidation is now being used clinically to treat ischemic heart disease. For instance, trimetazidine is an antiangiinal agent that stimulates glucose oxidation in the heart secondary to an inhibition of fatty acid oxidation. Because of the controversy about whether fatty acid oxidation inhibition or stimulation is desirable in obesity, it is important to clarify what effect these fatty acid oxidation inhibitors have on cardiac function and metabolism in these pathologies.

Circulating Fatty Acids and Cardiac Pathology in Obesity

High levels of plasma fatty acids can contribute to impairment of cardiac function in diabetes. Furthermore, in diabetic patients without heart disease, increased plasma fatty acid levels are positively correlated with a decrease in cardiac energy metabolism, as measured by cardiac phosphocreatine/ATP ratios. However it is not known whether this relationship is causal or whether elevated fatty acids directly and adversely affect cardiac function in diabetic patients. Elevated plasma fatty acid levels are also modestly correlated with a decreased diastolic function (r=0.33) in severely obese patients, but, again, a causal role of fatty acids or cardiac lipid accumulation in diastolic dysfunction has not been demonstrated. Experimental studies in the perfused rat and mouse hearts have also shown that accelerated fatty acid
oxidation contributes to the development of diabetic cardiomyopathies by inhibiting glucose oxidation and lowering cardiac mechanical efficiency and that pharmacologically inhibiting fatty acid metabolism and increasing glucose metabolism improves contractile function in diabetes. This is supported by clinical studies in which the use of the fatty acid oxidation inhibitor trimetazidine improves heart function in diabetic patients with ischemic cardiomyopathies.

The mechanism(s) by which fatty acids contribute to cardiac pathology has not been completely delineated. Fatty acid inhibition of myocardial glucose use appears to be one important contributing factor. Exposure of the heart to high levels of fatty acids can cause accumulation of lipids, ie, “cardiac lipotoxicity.” This general concept of cellular lipotoxicity argues that excessive accumulation of lipids within nonadipose tissue increases the intracellular pool of long-chain fatty acyl-CoA, thereby providing fatty acid substrate for nonoxidative processes, including triacylglycerol, diacylglycerol, and ceramide synthesis, which can lead to cell dysfunction, insulin resistance, and potentially apoptotic cell death. Results from studies in nonobese transgenic mice and rat models of obesity and diabetes show that the accumulation of lipids and related intermediates (eg, ceramides) in cardiomyocytes is associated with impaired systolic contractile function, an increase in the end-diastolic volume of the left ventricle, and cardiac hypertrophy. It has been proposed that storage of intracellular triacylglycerol is protective under conditions of extracellular lipid overload caused by lower cytosolic long-chain fatty acyl-CoA levels and less formation of ceramides and other toxic lipid intermediates; however, it has also been suggested that elevated cardiomyocyte triglyceride stores exert a toxic effect through providing a readily available source of cytosolic long-chain fatty acyl-CoA.

The potential for cardiac lipotoxicity in obesity has also recently been suggested. We have shown that insulin-resistant rat hearts have elevated triacylglycerol content, which is associated with a decrease in glucose uptake and glycolysis. However, the relative importance of an increase in fatty acid supply versus a decreased fatty acid oxidative capacity as the major contributor to lipotoxicity is unclear in these models. It has been proposed that downregulation of PPARα and/or a decrease in PPARα responsiveness in obesity results in underexpression of fatty acid oxidative enzymes, accumulation of intracellular lipids, and development of cardiomyopathy. As discussed above, studies of obese/insulin-resistant human and rodent hearts have not observed decreases in fatty acid oxidation, but rather the opposite. Recent studies in a transgenic mouse model of the metabolic syndrome suggest that cardiac mitochondrial biogenesis is increased in obesity because of fatty acid activation of PPARα/PPARγ coactivator-1α. Obese mice have normal activity of fatty acid oxidation enzymes, impaired expression of key components of the electron transport chain, decreased mitochondrial coupling, and poor cardiac mechanical efficiency, suggesting that maintained expression of fatty acid oxidation enzymes may act to compensate for mitochondrial inefficiency.

Lipid-Induced Alterations in Insulin Signaling in the Heart

Insulin effects on glucose uptake, glycolysis, and protein synthesis, begin with insulin binding to the insulin receptor and a stimulation of tyrosine phosphorylation of the insulin receptor substrate-1. This initiates a cascade of events, including activation of phosphatidylinositol 3-kinase and protein kinase B/Akt. Insulin resistance results in a number of changes in the insulin signaling cascade, including inhibition of insulin-stimulated tyrosine phosphorylation of insulin receptor substrate-1, associated phosphatidylinositol 3-kinase activity, decreased protein kinase B phosphorylation, and decreased glycogen synthase kinase-3 and p70S6K phosphorylation. Fatty acid–induced changes in insulin signaling is a potentially important determinant of these alterations in insulin sensitivity. Accumulation of diacylglycerol is thought to activate protein kinase C, resulting in a serine kinase cascade that increases insulin receptor substrate-1 phosphorylation and leading to a decrease in phosphatidylinositol 3-kinase activity, decreased Akt activity, and decreased glucose uptake.

Adipokine Regulation of Myocardial Metabolism

Over the last decade, much evidence has accumulated regarding the role of adipose tissue as an endocrine organ and the secretion of adipokines (eg, leptin, adiponectin, resistin, ghrelin, visfatin) that act on nonadipose tissues, such as the heart, to produce diverse cellular and whole-animal functions, including alterations in fat metabolism and cell growth. Obesity affects the secretion of adipokines, specifically increasing leptin and decreasing adiponectin, which can impact the heart and vascular system.

Adiponectin Regulation of Myocardial Metabolism

The original identification of adiponectin occurred simultaneously in independent groups from either the human cDNA project or cloning of the mouse homolog, known as ACRP30 and AdipoQ. It is one of the most abundant serum proteins (3 to 30 µg/mL) and occurs in 3 major oligomeric forms (trimer, hexamer, and high-molecular-weight form) in human and mouse plasma. Serum levels of adiponectin are significantly lower in obese patients compared with nonobese controls and are inversely correlated with body mass index. The heart expresses the 3 currently identified adiponectin receptors, AdipoR1, AdipoR2, and T-cadherin, suggesting there is a direct effect of adiponectin in the heart (Figure 2).
Although there is consensus that adiponectin stimulates fatty acid oxidation in skeletal muscle via an AMPK signaling mechanism, the role of adiponectin in the heart is unclear. Plasma adiponectin levels rise dramatically in the maturing newborn rabbit; however, when 1-day-old rabbit hearts were perfused in the presence of adiponectin (10 μg/mL), there were no observed effects on fatty acid oxidation. In contrast, when hearts were perfused in the presence of globular adiponectin (gAd) (1.5 μg/mL, the globular head domain of adiponectin), fatty acid oxidation was stimulated, however, via an AMPK/ACC-independent signaling mechanism. Addition of insulin reversed the effect of gAd on myocardial metabolism, suggesting interplay between gAd and phosphorylation of p38, ACC, and PPARα signaling.

We have also observed that adiponectin stimulates fatty acid oxidation in rat neonatal cardiac myocytes infected with adenovirus containing a dominant-negative AMPK, whereas the adiponectin effect is attenuated in myocytes infected with constitutively active AMPK. Associated with the increase in fatty acid oxidation is increased phosphorylation of p38 (attenuated with the dominant-negative AMPK) and p42/44 (maintained with dominant-negative AMPK), suggesting both AMPK-dependent and -independent signaling pathways. In addition, preliminary studies in isolated working mouse hearts have shown that adiponectin and gAd are unable to activate AMPK (D. Morabito, J. Y. Altarejos, and G.D.L., unpublished results, 2007). Physiological concentrations of human recombinant gAd transiently activate AMPK and phosphorylation of p38, ACC, and PPARα and increase CPT1 mRNA and activity in neonatal rat ventricular myocytes. These downstream signaling effects were blocked by 9-β-D-arabinofuranoside, a nonspecific AMPK inhibitor, and SB202190, a specific p38 inhibitor, suggesting that gAd activation of AMPK may stimulate fatty acid oxidation via both an increase in CPT1 activity and a decrease in malonyl-CoA inhibition of CPT1 activity. Direct evidence for adiponectin-induced changes in malonyl-CoA levels or fatty acid oxidation has not been provided.

Taken together, these studies suggest that adiponectin can accelerate fatty acid oxidation in the heart and, under some conditions, may lead to activation of AMPK and its downstream targets. This lack of consistent activation of AMPK may be attributable to the formulation of adiponectin used, as Shibata et al showed that only the trimer form of adiponectin can activate AMPK in a primary culture of rat neonatal cardiac myocytes. This may be explained by the fact that gAd has higher binding affinities to the membrane fractions of muscle than full-length adiponectin. The significance of these findings to obesity is not presently clear, because adiponectin levels are decreased in obese subjects, yet fatty acid oxidation rates are high.

**Adiponectin and Cardioprotection**

There is evidence that adiponectin may play an important role in cardiac pathologies including LV hypertrophy and ischemia/reperfusion injury. Compared with wild-type animals, adiponectin-knockout mice show enhanced concentric LV hypertrophy and mortality following aortic banding, which is associated with increased activation of extracellular signal-regulated kinase and reduced AMPK activation. In addition, adenovirus-mediated supplementation of adiponectin partially prevents cardiac hypertrophy in response to aortic banding. Despite these apparent protective effects of adiponectin on hypertrophic cardiomyopathy, a previous clinical study has demonstrated that high adiponectin levels are associated with an increase in the risk of mortality in patients with congestive heart failure.

Adiponectin may also have a protective effect in ischemia/reperfusion, as adiponectin-knockout mice develop larger infarcts, which are associated with increased tumor necrosis factor-α expression and myocyte apoptosis. Adenoviral delivery of adiponectin before, during, or following ischemia results in a reduction in infarct size, which is blocked with the use of a dominant-negative AMPK, suggesting that the prosurvival mechanism is mediated by AMPK signaling. Adiponectin has been suggested to produce this protective effect via activation of cyclooxygenase-2 (COX-2) in cardiac myocytes, as inhibition of this enzyme partially reversed the cardioprotective effects of adiponectin. Adiponectin may also exert anti-ischemic effect through stimulation of angiogenesis, and by increasing endothelial NO production through stimulation of endothelial NO synthase by an AMPK-dependent mechanism and thus should favorably impact microvascular function. Although the precise details of this effect are not fully understood, these observations support a role for adiponectin in protecting the heart during ischemic episodes.
mechanisms remain to be determined, there is growing evidence that adiponectin plays a protective role in the heart following ischemic stress or with chronic pressure overload.\textsuperscript{151}

**Leptin Regulation of Myocardial Metabolism**

Leptin, the 16 kDa obese gene product, was originally identified in 1994\textsuperscript{41} and is positively correlated with the percentage body fat in patients.\textsuperscript{152} Originally considered to be an obesity signal to the central nervous system to maintain energy balance, the localization of leptin receptors on a variety of peripheral tissues suggests a wide range of actions. Leptin receptors Ob-Ra, Ob-Rb, and Ob-Re have all been identified in mouse heart homogenates, suggesting that leptin has direct effects on the heart (Figure 2).\textsuperscript{153}

Our laboratory has previously shown that in isolated working rat hearts, leptin (60 ng/mL) increases exogenous and endogenous fatty acid oxidation, with no change in glucose oxidation.\textsuperscript{119} This increase of fatty acid oxidation is associated with a decrease in triacylglycerol content and an increase in myocardial oxygen consumption, thus decreasing cardiac efficiency. However, in contrast to what is observed in skeletal muscle, this does not occur via activation of the AMPK/ACC/malonyl-CoA axis, and the increase in fatty acid oxidation may be attributable to increased activity of mitochondrial uncoupling protein. Interestingly, similar to what is observed with adiponectin, coadministration of insulin blocks the leptin-induced increase in fatty acid oxidation.

Recently Palanivel et al demonstrated that in HL-1 cardiomyocytes, short-term (1 hour) and long-term (24 hour) leptin (60 nmol/L) treatment does not modify glucose uptake and oxidation or glycogen synthesis.\textsuperscript{154} Short-term leptin treatment significantly increases fatty acid oxidation (associated with decreased intracellular lipid content); however, after 24 hours of treatment, fatty acid oxidation is impaired (and intracellular lipid is increased). These alterations in fatty acid oxidation correlate with increased phosphorylation of AMPK and ACC after 1 hour but no difference after 24 hours. In addition, there was no effect of insulin on leptin treatment.

Other studies have looked at the effects of leptin treatment on glucose uptake in the heart. Administration of leptin via either intravenous or intracerebroventricular infusion produces a significant increase in glucose uptake in skeletal muscle; however, there is no observed effect in the heart.\textsuperscript{155} Yet, in a Langendorff perfused rat heart, a dose of 1 ng/mL leptin produces a significant increase in glucose uptake.\textsuperscript{156} Of interest is that ischemia causes a downregulation of leptin and leptin receptor gene expression, which suggests there may be an interesting link between ischemic heart disease and leptin; however, further studies are required to better delineate this link.\textsuperscript{157} Two experimental studies have examined the effects of ischemia/reperfusion on leptin and leptin receptor gene expression with conflicting results. Purdham et al showed a clear downregulation of both leptin and leptin receptor (gene expression in isolated rat hearts), with no effect on leptin efflux.\textsuperscript{157} In contrast, a recent study suggests that there is increased expression of leptin and OB-Ra and decreased expression of OB-Rb gene expression following in vivo left coronary artery ligation and reperfusion.\textsuperscript{158} The clinical data are also conflicting, as a study of French Canadian men showed no association between leptin and coronary heart disease, whereas a large Scottish prospective study identified leptin as a independent risk factor for coronary heart disease in men and a Swedish study showed that elevated leptin levels is an effective predictor of first-ever myocardial infarction.\textsuperscript{159–161}

Although few studies have directly looked at the effect of leptin on myocardial metabolism, the effect of leptin can be inferred from studies of genetic models of leptin deficiency/leptin resistance, such as the Zucker fatty rat and the ob/ob and db/db mice. The Zucker fatty rat has a missense mutation in the leptin receptor gene that causes a phenotype of increased fat pad mass, hyperlipidemia, and hyperinsulinemia.\textsuperscript{162} Adipocytes from Zucker rats have increased fatty acid utilization, and it was later shown that cardiomyocytes also have increased uptake of fatty acids because of an increase in fatty acid transporters (CD36 and FABPpm) in the plasma membrane.\textsuperscript{50,163} These effects mostly likely are caused by elevated circulating fatty acids and triacylglycerol, not by the leptin resistance; however, when hearts from Zucker rats were perfused as working hearts, they showed an impaired fatty acid oxidation and a decrease in glucose oxidation in response to fasting compared with lean controls.\textsuperscript{49} In addition, when ob/ob and db/db were perfused as working hearts at 4 weeks of age (before the onset of hyperglycemia), both models had a significant increase in fatty acid oxidation and decrease in glucose oxidation compared with wild-type controls.\textsuperscript{52} This increase in fatty acid oxidation occurs independent of changes in insulin signaling and PPAR\textsubscript{\alpha} transcriptional regulation but may be attributable to increased fatty acid transport proteins on the plasma membrane. Therefore in the genetic models of leptin deficiency/resistance, it is difficult to delineate the direct effects of leptin on the heart from the compensatory effects of the genetic mutation.

**Obesity, Metabolism, and Cardiac Disease:**

**Clinical Implications**

It is well established that obesity increases the risk for cardiovascular disease,\textsuperscript{164} specifically myocardial infarction\textsuperscript{165} and heart failure.\textsuperscript{2} Much of the increase in cardiovascular disease in obese patients stems from a greater frequency of risk factors that are the result of obesity (eg, hypertension, dyslipidemia, insulin resistance, diabetes).\textsuperscript{166} Nevertheless, epidemiological evidence suggests that obesity persists as an independent risk factor for ischemic heart disease and heart failure after correction of known risk factors.\textsuperscript{2,164,165} The physiological mechanisms linking obesity with cardiac disease are poorly characterized but may involve adipokine signaling, altered insulin signaling, and changes in circulating glucose and lipids. Leptin is a potential mediator of cardiac hypertrophy in obesity,\textsuperscript{167} possibly by causing an increase in sympathetic vasoconstrictor tone and arterial blood pressure\textsuperscript{168,169} or through direct stimulation of protein synthesis in cardiomyocytes.\textsuperscript{170,171} On the other hand, studies in rat and mouse models of obesity suggest that leptin has a protective effect on the heart.\textsuperscript{9,111,172–175} It has been proposed that the hyperleptinemia that occurs in most forms of obesity/overnutrition is protective to the heart through suppression of food
intake mediated through the hypothalamic appetite centers and upregulation of fatty acid oxidation and reduction of lipid storage and formation of toxic lipid compounds in the heart. Another possible mediator of the link between obesity and cardiac disease is the decrease in plasma adiponectin concentration in this population. Low adiponectin levels may impair the ability of the heart to adapt optimally to acute and chronic stress, as suggested from studies of adiponectin deficiency in mice in which there is greater ventricular hypertrophy and contractile dysfunction in response to pressure overload and increases in postischemic injury compared with mice with normal adiponectin levels. Epidemiological studies, however, did not find a relationship between the low adiponectin levels in obese people and the incidence of ischemic heart disease or heart failure.

The hyperinsulinemia that is frequently observed in obese patients may contribute to the development of LV hypertrophy, perhaps through insulin activation of cardiac protein synthesis and inhibition of protein breakdown. On the other hand, it has also been proposed that cardiac insulin resistance with obesity may lead to cardiac dysfunction and contribute to the development of heart failure. At present, it is not known whether the systemic insulin resistance and elevated insulin concentrations frequently observed in obesity trigger cardiac hypertrophy and/or ventricular remodeling and dysfunction. Long-term interventional studies are needed to assess the links among obesity, metabolic hormones, circulating substrates, and cardiac diseases.

Paradoxically, obesity has either a protective or neutral effect on the outcome from acute ischemic events and revascularization procedures and also predicts reduced mortality in heart failure patients compared with those who are normal weight. These unexpected associations may not be causal and may be confounded by the younger age of the obese patients in most of these studies and the masking of symptoms by the limited capacity for physical exercise in obese patients. In any case, there is no evidence that obesity or elevated plasma triacylglycerol or cholesterol increases risk of death from a given acute ischemic event or in patients with diagnosed heart failure.

The development of heart failure in the obese population may involve different pathophysiological mechanisms than in nonobese heart failure patients. The presentation of heart failure in obese people is associated with a cluster of obesity-related pathogenic factors (eg, elevated circulating free fatty acids and glucose, suppressed adiponectin levels, elevated insulin and leptin, etc) that are not generally found in nonobese heart failure patients. As discussed above, the hyperlipidemia that frequently accompanies obesity may increase cardiac lipid uptake and formation of ceramide and other toxic lipids, and upregulate the expression of proteins involved in myocardial fatty acid metabolism via stimulation of PPAR activity, and switch the balance of fuel metabolism by the heart toward greater fatty acid oxidation and less carbohydrate oxidation, resulting in oxygen wasting and lower cardiac mechanical efficiency. In addition, impaired pyruvate oxidation in the face of normal or accelerated glucose uptake could result in greater flux through the hexosamine biosynthesis pathway, the pentose phosphate shunt (which can generate reactive oxygen species and lipid peroxidation), or formation of advanced glycosylation end products, which all could potentially impair cardiac energy metabolism, contractility, and diastolic function. On the other hand, it is possible that some of the metabolic and/or hormone differences between normal-weight and obese heart failure patients are cardioprotective, such as elevated leptin. In any case, there is increasing evidence to suggest that the metabolic and hormonal abnormalities in obesity not only contribute to a greater occurrence of heart failure in this population but may also generate a less malignant form of this syndrome.

There is little outcomes-based evidence regarding how dietary macronutrient composition affects cardiac function or the development of heart failure in normal-weight or obese people. The first-line treatment for obesity is reduction of caloric intake; however, the exact manner in which to do this remains controversial, and the optimal “cardioprotective” weight loss or maintenance diet for obese patients with either ischemic heart disease, heart failure, or hypertension is not established. Recent epidemiological studies found no decrease in the incidence of coronary heart disease with reduced fat intake but actually a reduction in risk with a relatively high-fat diet rich in polyunsaturated fatty acids or lipids of vegetable origin. Even less consideration has been given to the potential adverse effects of diets high in sugar and rapidly digested starch, which could adversely affect the heart by numerous mechanisms. Recent studies in hypertensive rats suggest that LV dysfunction and remodeling is slowed when a low-carbohydrate/high-fat diet is consumed and is accelerated by diets high in sugar; however, the mechanisms responsible for these effects are unclear. At present, the optimal dietary composition of fat and carbohydrate for cardioprotection in patients with cardiac disease or hypertension is unclear, particularly in the patient with concomitant obesity. Nevertheless, there is growing evidence that diets that are relatively high in fat, particularly omega-3 fatty acids, and low in sugar may be protective.

Conclusions

An overreliance of the heart on fatty acid oxidation and accumulation of intracellular lipids contributes to the increased prevalence of cardiomyopathies in the obese population. An increase in myocardial reliance on fatty acids in obesity may also have detrimental consequences in the ischemic heart. Further studies should clarify the mechanisms that regulate cardiac fatty acid metabolism in obesity and identify nutritional and pharmacological interventions to prevent the adverse effects of obesity on the heart. On the other hand, the paradoxical protective effects of obesity in established heart failure may provide insights into novel cardioprotective therapies, thus warranting further investigation. Our understanding of the effect of obesity on cardiac function and metabolism is greatly limited by the paucity of human data, particularly relating to the effects of comorbidities (insulin resistance, diabetes, hypertension, hyperlipidemia) in this population. Future studies should hopefully clarify how these comorbidities contribute to obesity-induced cardiomyopathies.
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None.

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