Journal of the American College of Cardiology
© 2008 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 51, No. 2, 2008
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2007.10.021

STATE-OF-THE-ART PAPER

Insulin-Resistant Cardiomyopathy

Clinical Evidence, Mechanisms, and Treatment Options

Ronald M. Witteles, MD, Michael B. Fowler, MB, FACC
Stanford, California

Increasing evidence points to insulin resistance as a primary etiologic factor in the development of nonischemic heart failure (HF). The myocardium normally responds to injury by altering substrate metabolism to increase energy efficiency. Insulin resistance prevents this adaptive response and can lead to further injury by contributing to lipotoxicity, sympathetic up-regulation, inflammation, oxidative stress, and fibrosis. Animal models have repeatedly demonstrated the existence of an insulin-resistant cardiomyopathy, one that is characterized by inefficient energy metabolism and is reversible by improving energy use. Clinical studies in humans strongly support the link between insulin resistance and nonischemic HF. Insulin resistance is highly prevalent in the nonischemic HF population, predates the development of HF, independently defines a worse prognosis, and predicts response to antiadrenergic therapy. Potential options for treatment include metabolic-modulating agents and antidiabetic drugs. This article reviews the basic science evidence, animal experiments, and human clinical data supporting the existence of an "insulin-resistant cardiomyopathy" and proposes specific potential therapeutic approaches. (J Am Coll Cardiol 2008;51:93–102) © 2008 by the American College of Cardiology Foundation

Insulin resistance, often manifested clinically through the features of the metabolic syndrome or type II diabetes mellitus, has reached epidemic levels in the U.S. and many nations throughout the world (1,2). Heart failure (HF) will eventually affect 1 in 5 Americans and is responsible for the consumption of an extraordinary proportion of health care resources (3–5). Although a relationship between these 2 diseases has been long-recognized, it has classically been attributed to the increased prevalence of myocardial ischemia in patients with insulin resistance and to the fact that HF itself causes whole-body insulin resistance (6,7). We propose a more fundamental link between insulin resistance and HF, one independent of coronary artery disease (Fig. 1). The theories/evidence for this link as well as potential treatment options will be reviewed in this article.

Clinical Evidence

A link between insulin resistance and HF has been noted for more than a century. In 1881, Leyden (8) noted that HF is a "frequent and noteworthy complication of diabetes mellitus," and Mayer (9,10) speculated 7 years later that "heart disease in diabetes can be traced to an abnormality in metabolism." In 1974, Kannel et al. (11) found that men with cardiomyopathy were more than twice as likely as matched control subjects to have diabetes mellitus, with women more than 5 times as likely. Surprisingly, this link between diabetes and HF actually grew stronger when patients with ischemic heart disease were excluded. Other descriptions of a specific "diabetic cardiomyopathy" continued to emerge in the 1970s (12,13).

Subsequent studies have confirmed the existence, at the very least, of a strong correlation between diabetes and nonischemic cardiomyopathy, with a dramatically increased prevalence of diabetes in the dilated cardiomyopathy population (12,14–21). In newly diagnosed patients with HF, this increase in prevalence might be up to 4 times as high (14). Each 1% increase in hemoglobin A1c is associated with an 8% increased risk of HF, even after adjusting for other factors, including coronary artery disease (22). Importantly, the increased prevalence of abnormal structure and frank HF is seen with insulin resistance even when not accompanied by frank diabetes mellitus (18,21–23). Patients with nonischemic cardiomyopathy are not only more insulin-resistant than a healthy control population but also are more insulin-resistant than patients with coronary artery disease (24).

Abnormalities in diastolic function independent of ischemic heart disease are very commonly observed in patients with insulin resistance and diabetes mellitus and can be favorably impacted by improved glycemic control (25,26). Hypertension, left ventricular hypertrophy, and left ventricular dysfunction are strongly correlated with insulin resistance and the subsequent development of HF (17,18, 27–29).

From the Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California. Dr. Witteles has received financial support for studies of insulin-resistant cardiomyopathy from the Heart Failure Society of America.

Manuscript received June 15, 2007; revised manuscript received October 4, 2007, accepted October 22, 2007.

Abbreviations and Acronyms

ATP = adenosine triphosphate

DPP = dipeptidyl peptidase

FFA = free fatty acid

GLP = glucagon-like peptide

GLUT = glucose transporter

HF = heart failure

IRCM = insulin-resistant cardiomyopathy

LVEF = left ventricular ejection fraction

PPAR = peroxisome proliferator-activated receptor

TZD = thiazolidinedione

VO_{2max} = peak oxygen consumption

We have examined the prevalence of subclinical insulin resistance in patients with nonischemic cardiomyopathy compared with a matched control population, excluding patients with known pre-existing diabetes. The cardiomyopathy population was not only significantly more insulin resistant than matched control subjects (Fig. 2) but also had a very high prevalence of frank glucose dysmetabolism when challenged with an oral glucose load (21). When patients with known diabetes were included, 59% of cardiomyopathy patients had frank glucose dysmetabolism (21), even higher than another study examining a mixed ischemic/nonischemic population, which found a prevalence of 43% (19).

Epidemiological evidence suggests more than simply a correlation between insulin resistance and HF, demonstrating that insulin resistance precedes HF rather than occurring as a consequence of it. A study of 1,187 Swedish patients without prior HF found that insulin resistance predicts the subsequent development of HF, independent of all established risk factors, including diabetes mellitus itself (18). Another study found higher proinsulin levels (a surrogate marker for insulin resistance) in patients who subsequently developed HF than in control patients 20 years before their HF was diagnosed (30).

Insulin resistance and diabetes portend a worse prognosis in HF. The prognostic impact of insulin resistance is independent of other variables, including peak oxygen consumption (VO_{2max}) and left ventricular ejection fraction (LVEF), implying that insulin resistance is pathogenic rather than simply a marker for worsened HF (19,31).

The presence/absence of diabetes mellitus is more than 7 times as potent a risk factor for mortality in the nonischemic cardiomyopathy population as in the ischemic population (4). Indeed, the highest-risk subgroup from a recent study was the diabetic/nonischemic population (relative risk [RR] 1.79 vs. the nondiabetic/nonischemic population), as compared with the nondiabetic/ischemic population (RR 1.07) or even the diabetic/ischemic population (RR 1.11) (4).

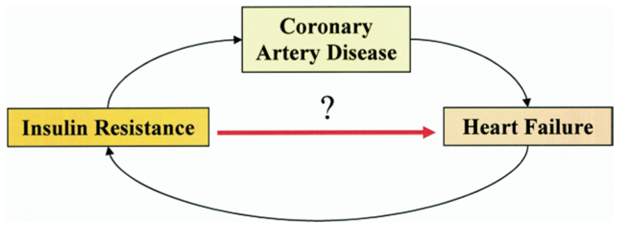

Figure 1 Relationships Between Insulin Resistance, Heart Failure, and Coronary Artery Disease

We propose a direct pathogenic mechanism linking insulin resistance to heart failure.

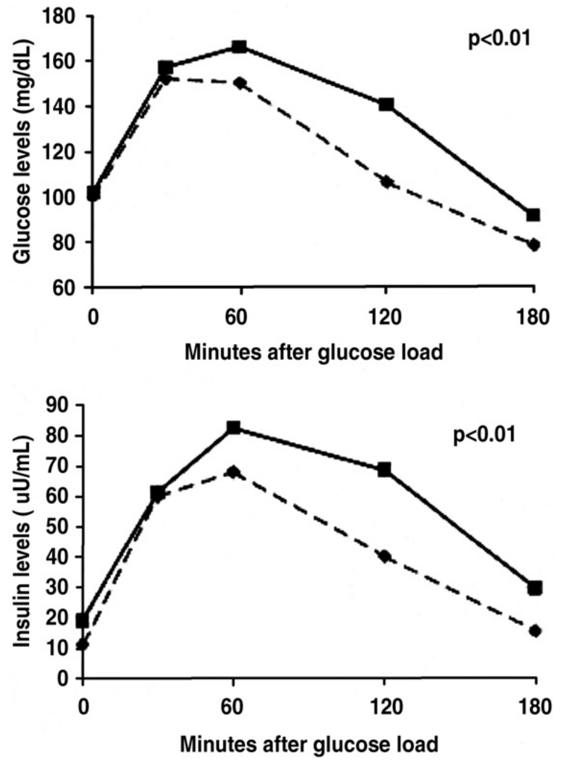

Figure 2 Glucose and Insulin Versus Time After Oral Glucose Load

Glucose **(top)** and insulin **(bottom)** versus time after oral glucose load for non-diabetic patients with nonischemic cardiomyopathy **(squares)** versus matched healthy control subjects **(diamonds)**. Note the baseline hyperinsulinemia and marked hyperglycemic/hyperinsulinemic responses to glucose loading in the heart failure population. Reproduced, with permission, from Witteles et al. (21).

Preliminary evidence also suggests that the presence of insulin resistance predicts response to therapy, especially antiadrenergic therapy. The potent adrenergic-blocking medication carvedilol, the only beta-blocker approved for HF that does not worsen insulin resistance, is 3 times as likely to cause a dramatic improvement in left ventricular function in the nonischemic cardiomyopathy population as in the ischemic cardiomyopathy population (32). Intriguingly, this degree of response to antiadrenergic therapy can be predicted by the severity of baseline abnormalities in myocardial glucose uptake (33).

Basic Mechanisms/Evidence

Insulin has profound effects on the myocardium, and its cellular mechanisms have been well-described. Although a complete description of the molecular pathways is beyond the scope of this article, a basic understanding is important to appreciate the potential effects of insulin resistance in the myocardium.

Binding of insulin to the insulin receptor results in autophosphorylation and activation of the receptor. The activated receptor then phosphorylates a docking protein that recruits phosphatidylinositol-3 kinase to the plasma membrane, which in turn activates the central mediator of insulin's effects, Akt-1 (also known as protein kinase B) (34).

Effects of Akt-1 activation independent of energy metabolism include inhibition of apoptosis, stimulation of myocyte hypertrophy/fibrosis, and nitric oxide production. Therefore, lack of insulin response can lead to less nitric oxide production (and potential endothelial dysfunction), more apoptosis, and alterations in myocardial structure (34–38).

Energy metabolism. Although response to insulin signaling affects many metabolic pathways, the most fundamental effects are on energy metabolism.

The heart is one of the most metabolically active organs in the body, needing to generate 5 kg of adenosine triphosphate (ATP)/day for contractile function and maintenance of cellular homeostasis and completely turning over its ATP supply every 13 s (34,39). To accomplish this goal, the heart metabolizes 3 fuels—free fatty acids (FFA), glucose, and (to a limited extent) lactate (34,40,41). The normal, unstressed adult heart predominantly uses FFA (approximately 70% of ATP production), owing to the high energy yield per molecule of substrate metabolized (42). However, in the stressed state (e.g., ischemia, pressure load, injury), the heart switches to the more efficient fuel, glucose. Efficiency in this context refers to the amount of ATP generated per molecule of oxygen consumed—the most relevant factor in the stressed state, in which the oxygen supply/demand ratio is altered (43). Glucose is the more efficient substrate for 2 reasons:

1. Stoichiometry: complete oxidation of FFA yields 12% less ATP/oxygen molecule consumed than complete oxidation of glucose (43).
2. Increased FFA levels (associated with peripheral insulin resistance) (25) promote synthesis of uncoupling proteins that dissipate the proton gradient across the inner mitochondrial membrane, resulting in production of heat rather than ATP (44–47). These 2 mechanisms combine for up to a 40% increase in ATP production per oxygen molecule consumed for glucose versus FFA.

Akt-1 activation has profound effects on energy metabolism, ultimately promoting the intracellular transport and metabolism of glucose (34,36,37). Conversely, Akt-1 both directly inhibits FFA metabolism and indirectly inhibits FFA metabolism by promoting glucose metabolism. When FFA supply is greater than the heart's oxidative capacity, FFA are stored as intramyocardial triglycerides, which are associated with lipotoxicity and worsened HF (42,48–55). Notably, the classic situation in which this can occur is in the state of insulin resistance—characterized by elevated circulating FFA levels—and the pattern of lipid deposition seen in animal models promoting FFA uptake is similar to that observed in patients with cardiomyopathy (42,55). Free fatty acids—whose circulating levels are elevated in individuals with insulin resistance—impair Akt-1 activation/insulin signaling, providing a positive feedback mechanism that can further the effects of insulin resistance (34,42). Because there is a great deal of "cross-talk" between metabolic pathways, inhibition of FFA metabolism promotes glucose metabolism and vice-versa (42,56,57).

The normal adaptive response by an injured/failing heart involves a complex series of enzymatic shifts and up-/down-regulation of transcription factors, ultimately resulting in increased glucose metabolism and decreased FFA metabolism to maximize efficiency (10,34,51,58–61) (Fig. 3). Although there is down-regulation of glucose transporters (GLUT)-1 and -4, this is overcome by down-regulation of pyruvate dehydrogenase kinase, an enzyme that normally decreases glucose oxidation (39,59,60). The net effect of these changes is an increase in glucose metabolism. In contrast, FFA metabolism is decreased, with decreased expression of the peroxisome proliferator-activated receptor (PPAR)-α/retinoid X receptor complex and 2 enzymes critical to FFA metabolism, carnitine palmitoyl transferase-1 and medium-chain acyl-coenzyme A dehydrogenase (10,39,51,58–60). To further maximize efficiency, uncoupling proteins are down-regulated in the failing heart (59).

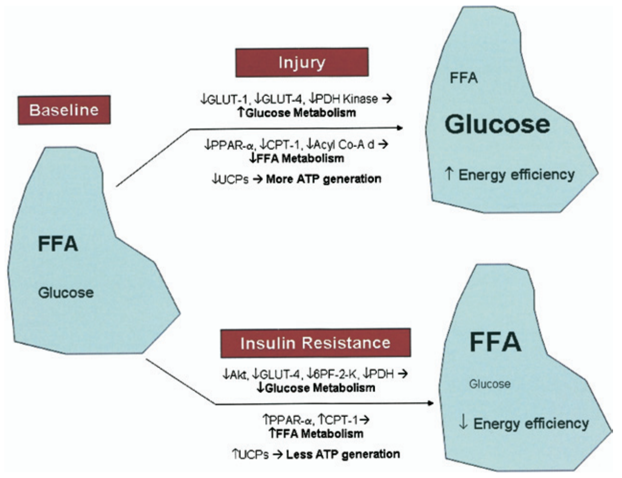

Figure 3 **Myocardial Energy Metabolism in Response to Injury/Insulin Resistance**

Relative size of font indicates relative metabolism of free fatty acids (FFA)/glucose. Acyl Co-A d = medium-chain acyl-coenzyme A dehydrogenase; CPT = carnitine palmitoyl transferase; GLUT = glucose transporter; PDH = pyruvate dehydrogenase; PPAR = peroxisome proliferator-activated receptor; UCP = uncoupling protein; 6PF-2-K = 6-phosphofructo-2-kinase.

These adaptive responses of the heart are inhibited in the setting of insulin resistance (Fig. 3). Although the initial myocardial metabolic switch in HF is down-regulation of FFA metabolism, the opposite occurs (up-regulation of FFA metabolism) in the setting of insulin resistance (60,62–64). This increased reliance on FFA metabolism leads to increased oxygen consumption, decreased cardiac efficiency, and the potential for lipotoxicity (42,50,62). Even in a non-HF human population, obesity and insulin resistance result in increased FFA use and decreased cardiac efficiency (65). Studies in non-HF populations have yielded conflicting results regarding myocardial glucose uptake with systemic insulin resistance, depending on whether glucose uptake is stimulated by systemic (66) or local (67) insulin administration. These findings support elevated systemic circulating FFA as a major cause of decreased myocardial glucose uptake in insulin-resistant individuals. In severe HF, myocardial insulin resistance results in decreased membrane translocation of GLUT-4 and decreased phosphorylation of Akt-1 and is associated with myocardial ATP depletion (68).

Investigations with nuclear imaging using glucose and fatty acid tracers confirm the increased metabolism of glucose with decreased metabolism of fatty acids in the subpopulation of the nonischemic dilated cardiomyopathy population who are relatively insulin-sensitive (58), whereas HF patients with diabetes mellitus have myocardial insulin resistance and decreased myocardial glucose uptake (69) (Fig. 4). The degree of abnormal FFA metabolism predicts both morphologic changes in the heart and worsened clinical outcomes (70).

Insulin resistance at its most fundamental level inhibits uptake and metabolism of glucose. It is likely this effect—preventing the heart from using its adaptive energy response to an insult—which contributes to HF and the vicious cycle of neurohormonal activation, serving to potentiate the myocardial dysfunction and further increasing energy requirements (10,25,34,39–42,56,58–60,69). The cardiomyopathic heart in the setting of insulin resistance is perhaps the worst of all possibilities for energy metabolism, as gene expression for metabolizing FFA is down-regulated owing to the cardiomyopathy and genes for metabolizing glucose are down-regulated owing to insulin resistance, preventing the heart from efficiently metabolizing either fuel (34,39,59,71,72).

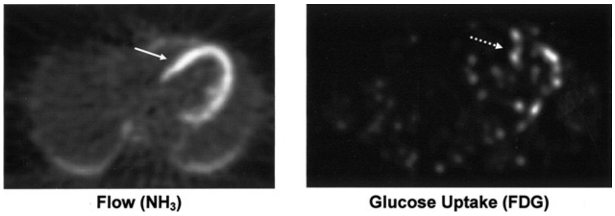

Figure 4 **Insulin Resistance and Abnormal Glucose Metabolism in Nonischemic Heart Failure Patients**

Myocardial perfusion **(left)** and glucose uptake **(right)** in a patient with idiopathic dilated cardiomyopathy and insulin resistance, as assessed by ^{13}N-ammonia (NH_3) and ^{18}F-fluoro-2-deoxyglucose (FDG) positron emission tomographic imaging. Note the strong, consistent signal in the left ventricle for blood flow **(solid arrow)** compared with the weak, scattered signal for glucose uptake **(dashed arrow)**, implying inefficient energy metabolism.

A series of elegant animal experiments has further defined the role of energy metabolism and insulin resistance in the pathogenesis of cardiomyopathy (Table 1). Importantly, some experiments have only been performed in diabetes mellitus and could be confounded by the effects of hyperglycemia. Underexpressing PPAR-α, which results in increased glucose metabolism and decreased FFA metabolism, prevents the development of a diabetic cardiomyopathy; overexpression of PPAR-α causes a more severe cardiomyopathy (50,53,73). Lowering the dietary fat content in animals who overexpress PPAR-α prevents the cardiomyopathy development, providing further evidence that the increased FFA metabolism is pathogenic (50). In contrast, treatment with the insulin-sensitizing PPAR-γ agonists results in more glucose metabolism, less FFA metabolism, and protection against development of a cardiomyopathy (50,53,55,74,75). Treatment with dichloroacetate (76), an agent that promotes glucose oxidation, or with etomoxir (77), an agent that inhibits a key enzyme in FFA metabolism, prevents the development of a cardiomyopathy in diabetic hearts. Selective knockout of the myocardial insulin receptor does not cause HF in isolation but leaves animals vulnerable to the addition of an additional insult (e.g., increased afterload) (78,79).

Insulin-resistant db/db and ob/ob mice preferentially metabolize FFA rather than glucose and predictably develop a severe nonischemic cardiomyopathy (80,81). Intriguingly, both the altered metabolism and the cardiomyopathy can be prevented with simultaneous overexpression of GLUT-4 (80,82). Other experimental techniques that increase FFA uptake cause lipotoxicity and a nonischemic cardiomyopathy, strongly implying a pathogenic role (48,54,83). Importantly, cardiac dysfunction precedes the development of systemic hyperglycemia, implying that the altered cellular metabolism rather than systemic hyperglycemia is responsible for the cardiac dysfunction (81).

Other models confirm the fact that when GLUT-1 and/or -4 are overexpressed, animals are protected from myocardial injury; when they are underexpressed, animals are more susceptible to myocardial injury (84,85). Still other models of insulin resistance (leptin deficiency, high-sucrose feeding) result in less efficient hearts (86) or hearts with frank myocardial dysfunction (87–90). Treatment of insulin resistance in these models (with troglitazone, metformin, or exercise) prevents myocardial dysfunction, but therapy aimed at hyperglycemia itself without treating insulin resistance (sulfonylureas) has no effect (87–90).

Inflammation, oxidative stress, and microvascular dysfunction. Inflammatory mediators are up-regulated in HF. Multiple experiments have found potential pathological links for some of the mediators, and some models have found improvements in HF with their antagonism (91–93).

Table 1 Experimental Models for Interactions Among Insulin Resistance, Energy Metabolism, and Heart Failure

Model/Therapy	Metabolic Change	Result
Underexpression PPAR-α	↓FFA metabolism ↑Glucose metabolism	Protection from IRCM
Overexpression PPAR-α	↑FFA metabolism ↓Glucose metabolism	Promotes IRCM
Overexpression PPAR-α and high-fat diet	Lipotoxicity/myocardial TG accumulation	Promotes IRCM and reversible with diet change
PPAR-γ agonist therapy	↑Insulin sensitivity ↑Glucose metabolism	Prevents LV dysfunction with ischemic and nonischemic insults
Dichloroacetate therapy	↑Glucose metabolism	Prevents IRCM
GLUT-1 overexpression	↑Glucose metabolism	Protection from pressure-induced LV dysfunction
GLUT-4 overexpression	↑Glucose metabolism	Protection from IRCM
GLUT-4 knockout	↓Glucose metabolism	Promotes CM with hypoxic insult
Leptin deficiency	↑FFA metabolism ↓Glucose metabolism	LV dysfunction and ↓energy efficiency
db/db or ob/ob mice	↓Insulin sensitivity	Promotes IRCM
Etomoxir therapy	↓FFA metabolism ↑Glucose metabolism	Protection from IRCM
High-sucrose feeding	↑Insulin resistance	Promotes IRCM
Myocardial insulin receptor knockout	↓Insulin sensitivity ↓FFA metabolism ↑Glucose metabolism	Baseline LV dysfunction, profound LV dysfunction with pressure overload

CM = cardiomyopathy; FFA = free fatty acid; GLUT = glucose transporter; IRCM = insulin-resistant cardiomyopathy; LV = left ventricular; PPAR = peroxisome proliferator-activated receptor; TG = triglycerides.

Although human clinical trials of inflammatory mediator antagonists have been largely unsuccessful, this might be because these trials have targeted individual components of the inflammatory cascade (tumor necrosis factor-α, endothelin) rather than the underlying mediator of the inflammation, such as insulin resistance (94,95). Notably, insulin resistance is associated with the same up-regulation of inflammatory pathways as is seen in HF, and this can be countered with treatment with insulin-sensitizing medications (96,97).

Several experiments have suggested that diabetic cardiomyopathy might be partially caused by accumulation of reactive oxygen species and subsequent oxidative stress (98,99). Interestingly, a transgenic mouse model overexpressing the antioxidant protein metallothionein demonstrated protection against the development of a diabetic cardiomyopathy (99).

Even in patients with no known coronary artery disease, microvascular dysfunction and decreased coronary flow reserve can be present. Such findings have been demonstrated particularly in the insulin-resistant/diabetic cardiomyopathy population (100–102). In the absence of resting flow abnormalities, this is less likely to be a cause of resting left ventricular dysfunction but could contribute to left ventricular dysfunction with stress or exercise. In addition, a mismatch between coronary blood flow and myocardial glucose uptake has been demonstrated (66) (Fig. 4).

Counter-regulatory hormone up-regulation and sympathetic activity. Multiple counter-regulatory hormones (epinephrine, norepinephrine, glucagon, cortisol, growth hormone) are up-regulated in HF and likely play a role in furthering insulin resistance and altered glucose disposition (7,103,104). Up-regulation of catecholamines not only increases insulin resistance but also directly contributes to the pathogenesis of cardiomyopathy. Indeed, histological changes associated with a nonischemic diabetic cardiomyopathy (increased myocyte apoptosis, necrosis, and fibrosis) (13,16,35,105) are similar to those observed in states of catecholamine excess (beta-receptor overexpressing animal models, catecholamine infusion by minipump, pheochromocytomas) (25,106). Elevated catecholamine levels, often present in individuals with insulin resistance, antagonize insulin's actions and promote lipolysis, increasing circulating FFA levels and furthering insulin resistance (107). Insulin therapy can reduce catecholamine-induced myocardial damage in the heart, suggesting that resistance to insulin can further this damage (108). Adrenergic blockade with carvedilol reduces FFA use with improved myocardial efficiency (68,109). The likely mechanism for this finding is that chronic beta-receptor stimulation (characteristic of untreated HF) inhibits insulin-mediated glucose uptake and activation of the insulin receptor (110), a finding that suggests the mechanism for the dramatic benefit seen in many patients with "insulin-resistant cardiomyopathies" (RM Witteles and MB Fowler, unpublished observations, December 2007).

Potential Treatments

If insulin resistance is important to the pathogenesis of HF, it is possible that therapies directed toward improving insulin resistance could improve outcomes.

Many of the established therapies in HF are also known to improve insulin resistance, even in non-HF populations. Standard lifestyle recommendations (exercise, smoking cessation, weight loss) are all associated with improvements in insulin sensitivity (111–113). Exercise improves both outcomes and insulin sensitivity in the nonischemic HF population (114). Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and statins all exert favorable effects on glucose metabolism (115–117). Although beta-adrenergic blocking medications usually worsen insulin resistance, carvedilol has a neutral-to-slight insulin sensitizing effect (118,119). Whether this difference contributes to the reported improvements in outcomes for patients treated with carvedilol, compared with metoprolol, remains unclear (68,120).

More intriguing is the possibility of pharmacologic therapy aimed at altering insulin resistance itself. Such medications could target various points in the energy use pathway, lowering circulating FFA levels, inhibiting FFA cellular or mitochondrial uptake, inhibiting FFA beta-oxidation, or promoting glucose uptake and metabolism.

Currently, the most promising potential medical therapies can be divided into 2 broad categories—metabolic modulators and diabetic medications (Table 2).

Metabolic modulators. The agents in this group increase myocardial efficiency by increasing glucose metabolism and decreasing FFA metabolism. Interestingly, 3 of the agents are used as antianginals; it is by increasing energy efficiency that these agents are believed to produce their antianginal effect.

One of the most promising potential treatment agents is trimetazidine. This medication—currently available in Europe but not in the U.S.—works by inhibiting the final enzyme in beta-oxidation of FFA. Trimetazidine administration results in improved myocardial ATP/phosphocreatine levels, a marker for myocardial energy stores (121). A recent study in 65 HF patients revealed substantial improvements in LVEF, quality of life, and New York Heart Association functional class in the trimetazidine arm (122). Notably, the nonischemic cardiomyopathy group derived a much greater benefit than the ischemic cardiomyopathy subgroup—intriguing for a drug approved as an antianginal agent and supportive of the theory that much of the problem in nonischemic cardiomyopathy is inefficient energy use.

A second agent that works by inhibiting FFA metabolism is perhexiline. Like trimetazidine, perhexiline is also used as an antianginal agent in other countries but is not approved in the U.S. A recent double-blind, placebo-controlled clinical trial of perhexiline in 56 HF patients demonstrated substantial improvements in LVEF, $\text{V}\text{O}_{2\text{max}}$, and quality of life (123). Unfortunately, clinical use of this agent might be limited, owing to risks of hepatotoxicity and peripheral neuropathy.

Ranolazine is a third antianginal agent with potential as a metabolic modulator (124) and is approved in the U.S. Unfortunately, it might not be an ideal choice for 2 reasons:

1. Although ranolazine does cause a switch from FFA to glucose, the degree of this effect is relatively limited at physiologic levels. Its main mechanism of action involves lowering intracellular calcium levels via inhibition of a slow-inactivating sodium current.
2. Ranolazine is associated with QT prolongation, although increased rates of ventricular arrhythmias have not been observed (125).

L-carnitine is an essential cofactor of fatty acid metabolism, shuttling the end-products of peroxisomal fatty acid oxidation into the mitochondria and modulating the intramitochondrial acyl-coenzyme A/coenzyme A ratio. Although its main role is enhancement of FFA metabolism, experimental evidence also supports an enhancement of glucose metabolism. Several human and animal studies support a modest benefit in left ventricular energetics and function with L-carnitine administration (126–128). Administration of the related propionyl-L-carnitine to the injured rat myocardium results in improved functional recovery and glucose use, supporting the theory that L-carnitine's beneficial effects are due to its ability to increase glucose oxidation despite elevated FFA levels (126,128).

Table 2 Potential Treatments for Insulin-Resistant Cardiomyopathy

Medication	Mechanism	Other/Side-Effects
Metabolic modulators		
Trimetazidine	↓FFA metabolism	Not approved in U.S.
Perhexiline	↓FFA metabolism	Not approved in U.S., liver/neuro-toxicity
Ranolazine	↑Glu metabolism	Might not be primary mechanism, ↑QT interval
L-carnitine	↑FFA/Glu metabolism	
Diabetic medications		
Insulin	↑Ins	Hypoglycemia
Sulfonylureas	↑Ins	Hypoglycemia
Metformin	↑Ins sensitivity	Lactic acidosis (rare)
TZDs ("glitazones")	↑Ins sensitivity	Fluid retention/edema
GLP-1	↑Ins/↑Ins sensitivity	Very short half-life (1–2 min)
Exenatide	↑Ins/↑Ins sensitivity	Nausea/weight loss, subcutaneous injection
DPP-IV inhibitor	↑Ins/↑Ins sensitivity	

DPP = dipeptidyl peptidase; FFA = free fatty acid; GLP = glucagon-like peptide; Glu = glucose; Ins = insulin; TZD = thiazolidinedione.

Diabetic medications. If insulin resistance—the fundamental feature of most cases of type II diabetes mellitus—plays a principle role in the pathogenesis of dilated cardiomyopathy in many patients, then agents used to treat patients with diabetes mellitus might also be useful for the insulin-resistant cardiomyopathy (IRCM) population.

Medications that work primarily by improving insulin sensitivity (metformin, thiazolidinediones [TZDs]) might theoretically be the most attractive therapies. Metformin, the only biguanide approved in the U.S., prevents worsened glucose metabolism in a non-HF, insulin-resistant population and can improve calcium handling in myocytes (90,111). However, its use in HF patients is limited by the possible potential for lactic acidosis, and a recent myocardial imaging study showed no improvement in myocardial glucose uptake with metformin administration (74).

The same study did show increased myocardial glucose uptake with the administration of a TZD (74). These agents work by activating PPAR-γ, a transcription factor that promotes insulin sensitivity and decreases circulating FFAs. Interestingly, TZDs seem to affect the myocardium, despite the near-complete lack of PPAR-γ receptors in the myocardium, indicating that the effects on the myocardium are due to decreased circulating FFAs (42,129). As noted previously, TZDs have been extensively studied in animal models of IRCM, where they have been shown to both improve myocardial glucose uptake and prevent left ventricular systolic dysfunction. Unfortunately, their clinical utility in the HF population is limited, owing to their promotion of fluid retention/edema, an effect mediated via activation of amiloride-sensitive sodium channels in the collecting duct (130,131). Recent controversy has also arisen over a possible association between rosiglitazone (1 of 2 TZDs approved in the U.S.) and increased rates of myocardial infarction (132–134).

Insulin or insulin-secretagogues represent a potential class of antidiabetic agents that could be used to treat an IRCM population. A beneficial impact of these agents could theoretically be gleaned by directly promoting glucose metabolism and decreasing circulating FFAs. However, therapy with such agents has generally failed to inhibit IRCM in animal models (89) and is less attractive than the insulin-sensitizing agents, because it fails to address the underlying physiologic problem of insulin resistance and exposes the patient to the potential negative effects of hyperinsulinemia.

Recently, a new class of antidiabetic medications has been developed that act on the glucagon-like peptide (GLP)-1 pathway. Glucagon-like peptide-1 is 1 of 2 main "incretins" in the body—hormones that promote post-prandial insulin secretion and improved insulin sensitivity (135). In a pacing-induced cardiomyopathy model (a model in which depletion of energy is likely a central cause of the cardiomyopathy), infusion of GLP-1 resulted in improved left ventricular function, hemodynamic status, and efficiency (104). Unfortunately, GLP-1 is impractical as a pharmacological therapy, because it is rapidly degraded in vivo by dipeptidyl peptidase (DPP)-IV, resulting in a 1- to 2-min half-life. Another option, exenatide, shares 53% homology with GLP-1 and works as a partial agonist of the GLP-1 receptor (135). An alternative to administering a GLP-1 agonist is administering a DPP-IV antagonist. The first agent in this class, sitagliptin, was approved in the U.S. in October 2006, and several others are in development. To date, neither exenatide nor the DPP-IV inhibitors have been studied in the HF population.

Conclusions

Almost certainly, insulin resistance itself is not enough to cause dilated cardiomyopathy; the very fact that the vast majority of patients with insulin resistance do not develop dilated cardiomyopathies highlights this point. Rather, insulin resistance likely creates an environment in which the addition of another stressor (e.g., pressure/volume overload, drugs/toxins, tachycardia) is poorly tolerated and enough to "tip the balance" in favor of developing a cardiomyopathy (Fig. 5). Under these circumstances, the body's compensatory mechanisms (up-regulation of the renin-angiotensin-aldosterone system, catecholamines, vasopressin) are maladaptive and can further worsen the cardiomyopathy. Not surprisingly, patients with IRCM seem to be those who are most likely to achieve dramatic responses to beta-adrenergic blocking therapy, often with recovery of LVEF to normal or near-normal levels. By lowering the demand side of the supply/demand balance, these agents would be expected to achieve dramatic results in patients in whom the fundamental defect is an energy supply/demand mismatch due to inefficient energy substrate use.

Delineation and appreciation of the role of insulin resistance as a fundamental cause of nonischemic cardiomyopathy should allow for the development of new therapies

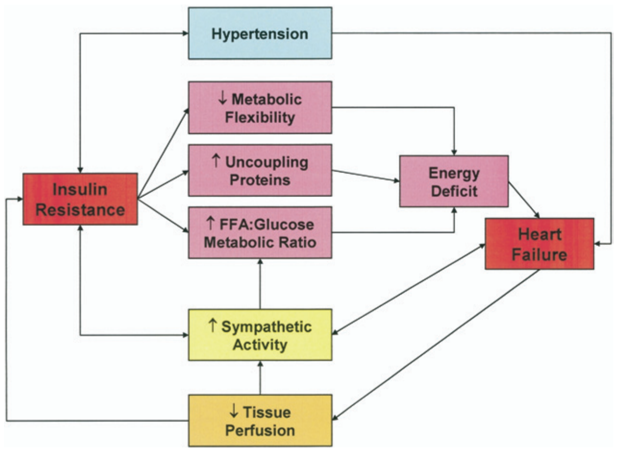

Figure 5 Relationships/Mechanisms Linking Insulin Resistance to Heart Failure

FFA = free fatty acids.

aimed at insulin resistance and metabolic modulation. Whether earlier identification and treatment of susceptible patients will be feasible and effective awaits further investigations and clinical trials.

Reprint requests and correspondence: Dr. Ronald M. Witteles, Division of Cardiovascular Medicine, Stanford University School of Medicine, 300 Pasteur Drive, Falk CVRC, Stanford, California 94305. E-mail: witteles@stanford.edu.

REFERENCES

1. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 2002;287:356–9.
2. Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002;288:2709–16.
3. Lloyd-Jones DM, Larson MG, Leip EP, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. Circulation 2002;106:3068–72.
4. From AM, Leibson CL, Bursi F, et al. Diabetes in heart failure: prevalence and impact on outcome in the population. Am J Med 2006;119:591–9.
5. Haldeman GA, Croft JB, Giles WH, Rashidee A. Hospitalization of patients with heart failure: National Hospital Discharge Survey, 1985 to 1995. Am Heart J 1999;137:352–60.
6. Wilson PW. Diabetes mellitus and coronary heart disease. Endocrinol Metab Clin North Am 2001;30:857–81.
7. Nikolaidis LA, Sturzu A, Stolarski C, Elahi D, Shen YT, Shannon RP. The development of myocardial insulin resistance in conscious dogs with advanced dilated cardiomyopathy. Cardiovasc Res 2004;61:297–306.
8. Leyden E. Asthma and diabetes mellitus. Zeutschr Klin Med 1881;3:358–64.
9. Mayer J. Ueber den zusammenhang des diabetes mellitus mit erkrankungen des herzens. Zeutschr Klin Med 1888;14:212–39.
10. Taegtmeyer H, Passmore JM. Defective energy metabolism of the heart in diabetes. Lancet 1985;1:139–41.
11. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol 1974;34:29–34.
12. Hamby RI, Zoneraich S, Sherman L. Diabetic cardiomyopathy. JAMA 1974;229:1749–54.
13. Regan TJ, Lyons MM, Ahmed SS, et al. Evidence for cardiomyopathy in familial diabetes mellitus. J Clin Invest 1977;60:884–99.
14. Amato L, Paolisso G, Cacciatore F, et al. Congestive heart failure predicts the development of non-insulin-dependent diabetes mellitus in the elderly. The Osservatorio Geriatrico Regione Campania Group. Diabetes Metab 1997;23:213–8.
15. Bertoni AG, Tsai A, Kasper EK, Brancati FL. Diabetes and idiopathic cardiomyopathy: a nationwide case-control study. Diabetes Care 2003;26:2791–5.
16. Coughlin SS, Pearle DL, Baughman KL, Wasserman A, Tefft MC. Diabetes mellitus and risk of idiopathic dilated cardiomyopathy. The Washington, DC Dilated Cardiomyopathy Study. Ann Epidemiol 1994;4:67–74.
17. Ingelsson E, Arnlov J, Lind L, Sundstrom J. Metabolic syndrome and risk for heart failure in middle-aged men. Heart 2006;92:1409–13.
18. Ingelsson E, Sundstrom J, Arnlov J, Zethelius B, Lind L. Insulin resistance and risk of congestive heart failure. JAMA 2005;294:334–41.
19. Suskin N, McKelvie RS, Burns RJ, et al. Glucose and insulin abnormalities relate to functional capacity in patients with congestive heart failure. Eur Heart J 2000;21:1368–75.
20. Vered A, Battler A, Segal P, et al. Exercise-induced left ventricular dysfunction in young men with asymptomatic diabetes mellitus (diabetic cardiomyopathy). Am J Cardiol 1984;54:633–7.
21. Witteles RM, Tang WH, Jamali AH, Chu JW, Reaven GM, Fowler MB. Insulin resistance in idiopathic dilated cardiomyopathy: a possible etiologic link. J Am Coll Cardiol 2004;44:78–81.
22. Iribarren C, Karter AJ, Go AS, et al. Glycemic control and heart failure among adult patients with diabetes. Circulation 2001;103:2668–73.
23. Ilercil A, Devereux RB, Roman MJ, et al. Associations of insulin levels with left ventricular structure and function in American Indians: the Strong Heart Study. Diabetes 2002;51:1543–7.
24. Swan JW, Anker SD, Walton C, et al. Insulin resistance in chronic heart failure: relation to severity and etiology of heart failure. J Am Coll Cardiol 1997;30:527–32.
25. Fang ZY, Prins JB, Marwick TH. Diabetic cardiomyopathy: evidence, mechanisms, and therapeutic implications. Endocr Rev 2004;25:543–67.
26. Schannwell CM, Schneppenheim M, Perings S, Plehn G, Strauer BE. Left ventricular diastolic dysfunction as an early manifestation of diabetic cardiomyopathy. Cardiology 2002;98:33–9.
27. 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.
28. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol 1993;22:6A–13A.
29. Verdecchia P, Reboldi G, Schillaci G, et al. Circulating insulin and insulin growth factor-1 are independent determinants of left ventricular mass and geometry in essential hypertension. Circulation 1999;100:1802–7.
30. Arnlov J, Lind L, Zethelius B, et al. Several factors associated with the insulin resistance syndrome are predictors of left ventricular systolic dysfunction in a male population after 20 years of follow-up. Am Heart J 2001;142:720–4.
31. Paolisso G, Tagliamonte MR, Rizzo MR, et al. Prognostic importance of insulin-mediated glucose uptake in aged patients with congestive heart failure secondary to mitral and/or aortic valve disease. Am J Cardiol 1999;83:1338–44.
32. O'Keefe JH Jr., Magalski A, Stevens TL, et al. Predictors of improvement in left ventricular ejection fraction with carvedilol for congestive heart failure. J Nucl Cardiol 2000;7:3–7.
33. Hasegawa S, Kusuoka H, Maruyama K, Nishimura T, Hori M, Hatazawa J. Myocardial positron emission computed tomographic images obtained with fluorine-18 fluoro-2-deoxyglucose predict the response of idiopathic dilated cardiomyopathy patients to beta-blockers. J Am Coll Cardiol 2004;43:224–33.
34. Shah A, Shannon RP. Insulin resistance in dilated cardiomyopathy. Rev Cardiovasc Med 2003;4 Suppl 6:S50–7.
35. Asbun J, Villarreal FJ. The pathogenesis of myocardial fibrosis in the setting of diabetic cardiomyopathy. J Am Coll Cardiol 2006;47:693–700.
36. Brazil DP, Hemmings BA. Ten years of protein kinase B signalling: a hard Akt to follow. Trends Biochem Sci 2001;26:657–64.
37. Lawlor MA, Alessi DR. PKB/Akt: a key mediator of cell proliferation, survival and insulin responses? J Cell Sci 2001;114:2903–10.
38. Stuhlinger MC, Abbasi F, Chu JW, et al. Relationship between insulin resistance and an endogenous nitric oxide synthase inhibitor. JAMA 2002;287:1420–6.
39. Taegtmeyer H. Switching metabolic genes to build a better heart. Circulation 2002;106:2043–5.
40. Taegtmeyer H, McNulty P, Young ME. Adaptation and maladaptation of the heart in diabetes: part I: general concepts. Circulation 2002;105:1727–33.
41. Young ME, McNulty P, Taegtmeyer H. Adaptation and maladaptation of the heart in diabetes: part II: potential mechanisms. Circulation 2002;105:1861–70.
42. An D, Rodrigues B. Role of changes in cardiac metabolism in development of diabetic cardiomyopathy. Am J Physiol Heart Circ Physiol 2006;291:H1489–506.
43. Opie L. The Heart: Physiology and Metabolism. New York, NY: Raven Press, 1991.
44. Boudina S, Sena S, O'Neill BT, Tathireddy P, Young ME, Abel ED. Reduced mitochondrial oxidative capacity and increased mitochondrial uncoupling impair myocardial energetics in obesity. Circulation 2005;112:2686–95.
45. Murray AJ, Anderson RE, Watson GC, Radda GK, Clarke K. Uncoupling proteins in human heart. Lancet 2004;364:1786–8.
46. Murray AJ, Panagia M, Hauton D, Gibbons GF, Clarke K. Plasma free fatty acids and peroxisome proliferator-activated receptor alpha

in the control of myocardial uncoupling protein levels. Diabetes 2005;54:3496–502.

47. Opie LH. The metabolic vicious cycle in heart failure. Lancet 2004;364:1733–4.
48. Chiu HC, Kovacs A, Ford DA, et al. A novel mouse model of lipotoxic cardiomyopathy. J Clin Invest 2001;107:813–22.
49. Christoffersen C, Bollano E, Lindegaard ML, et al. Cardiac lipid accumulation associated with diastolic dysfunction in obese mice. Endocrinology 2003;144:3483–90.
50. Finck BN, Han X, Courtois M, et al. A critical role for PPARalpha-mediated lipotoxicity in the pathogenesis of diabetic cardiomyopathy: modulation by dietary fat content. Proc Natl Acad Sci U S A 2003;100:1226–31.
51. Osorio JC, Stanley WC, Linke A, et al. Impaired myocardial fatty acid oxidation and reduced protein expression of retinoid X receptor-alpha in pacing-induced heart failure. Circulation 2002;106:606–12.
52. Pillutla P, Hwang YC, Augustus A, et al. Perfusion of hearts with triglyceride-rich particles reproduces the metabolic abnormalities in lipotoxic cardiomyopathy. Am J Physiol Endocrinol Metab 2005;288: E1229–35.
53. Vikramadithyan RK, Hirata K, Yagyu H, et al. Peroxisome proliferator-activated receptor agonists modulate heart function in transgenic mice with lipotoxic cardiomyopathy. J Pharmacol Exp Ther 2005;313:586–93.
54. Yagyu H, Chen G, Yokoyama M, et al. Lipoprotein lipase (LpL) on the surface of cardiomyocytes increases lipid uptake and produces a cardiomyopathy. J Clin Invest 2003;111:419–26.
55. Zhou YT, Grayburn P, Karim A, et al. Lipotoxic heart disease in obese rats: implications for human obesity. Proc Natl Acad Sci U S A 2000;97:1784–9.
56. Calvani M, Reda E, Arrigoni-Martelli E. Regulation by carnitine of myocardial fatty acid and carbohydrate metabolism under normal and pathological conditions. Basic Res Cardiol 2000;95:75–83.
57. Morrow DA, Givertz MM. Modulation of myocardial energetics: emerging evidence for a therapeutic target in cardiovascular disease. Circulation 2005;112:3218–21.
58. Davila-Roman VG, Vedala G, Herrero P, et al. Altered myocardial fatty acid and glucose metabolism in idiopathic dilated cardiomyopathy. J Am Coll Cardiol 2002;40:271–7.
59. Razeghi P, Young ME, Alcorn JL, Moravec CS, Frazier OH, Taegtmeyer H. Metabolic gene expression in fetal and failing human heart. Circulation 2001;104:2923–31.
60. Razeghi P, Young ME, Cockrill TC, Frazier OH, Taegtmeyer H. Downregulation of myocardial myocyte enhancer factor 2C and myocyte enhancer factor 2C-regulated gene expression in diabetic patients with nonischemic heart failure. Circulation 2002;106: 407–11.
61. Taegtmeyer H, Hems R, Krebs HA. Utilization of energy-providing substrates in the isolated working rat heart. Biochem J 1980;186: 701–11.
62. How OJ, Aasum E, Severson DL, Chan WY, Essop MF, Larsen TS. Increased myocardial oxygen consumption reduces cardiac efficiency in diabetic mice. Diabetes 2006;55:466–73.
63. Neitzel AS, Carley AN, Severson DL. Chylomicron and palmitate metabolism by perfused hearts from diabetic mice. Am J Physiol Endocrinol Metab 2003;284:E357–65.
64. Tuunanen H, Engblom E, Naum A, et al. Decreased myocardial free fatty acid uptake in patients with idiopathic dilated cardiomyopathy: evidence of relationship with insulin resistance and left ventricular dysfunction. J Card Fail 2006;12:644–52.
65. Peterson LR, Herrero P, Schechtman KB, et al. Effect of obesity and insulin resistance on myocardial substrate metabolism and efficiency in young women. Circulation 2004;109:2191–6.
66. Iozzo P, Chareonthaitawee P, Dutka D, Betteridge DJ, Ferrannini E, Camici PG. Independent association of type 2 diabetes and coronary artery disease with myocardial insulin resistance. Diabetes 2002;51: 3020–4.
67. Jagasia D, Whiting JM, Concato J, Pfau S, McNulty PH. Effect of non-insulin-dependent diabetes mellitus on myocardial insulin responsiveness in patients with ischemic heart disease. Circulation 2001;103:1734–9.
68. Nikolaidis LA, Poornima I, Parikh P, Magovern M, Shen YT, Shannon RP. The effects of combined versus selective adrenergic blockade on left ventricular and systemic hemodynamics, myocardial substrate preference, and regional perfusion in conscious dogs with dilated cardiomyopathy. J Am Coll Cardiol 2006;47:1871–81.
69. Dutka DP, Pitt M, Pagano D, et al. Myocardial glucose transport and utilization in patients with type 2 diabetes mellitus, left ventricular dysfunction, and coronary artery disease. J Am Coll Cardiol 2006; 48:2225–31.
70. Yazaki Y, Isobe M, Takahashi W, et al. Assessment of myocardial fatty acid metabolic abnormalities in patients with idiopathic dilated cardiomyopathy using 123I BMIPP SPECT: correlation with clinicopathological findings and clinical course. Heart 1999;81:153–9.
71. Taegtmeyer H, Ballal K. No low-fat diet for the failing heart? Circulation 2006;114:2092–3.
72. Tuunanen H, Engblom E, Naum A, et al. Free fatty acid depletion acutely decreases cardiac work and efficiency in cardiomyopathic heart failure. Circulation 2006;114:2130–7.
73. Finck BN, Lehman JJ, Leone TC, et al. The cardiac phenotype induced by PPARalpha overexpression mimics that caused by diabetes mellitus. J Clin Invest 2002;109:121–30.
74. Hallsten K, Virtanen KA, Lonnqvist F, et al. Enhancement of insulin-stimulated myocardial glucose uptake in patients with type 2 diabetes treated with rosiglitazone. Diabet Med 2004;21:1280–7.
75. Sidell RJ, Cole MA, Draper NJ, Desrois M, Buckingham RE, Clarke K. Thiazolidinedione treatment normalizes insulin resistance and ischemic injury in the Zucker fatty rat heart. Diabetes 2002;51: 1110–7.
76. Nicholl TA, Lopaschuk GD, McNeill JH. Effects of free fatty acids and dichloroacetate on isolated working diabetic rat heart. Am J Physiol 1991;261:H1053–9.
77. Wall SR, Lopaschuk GD. Glucose oxidation rates in fatty acid-perfused isolated working hearts from diabetic rats. Biochim Biophys Acta 1989;1006:97–103.
78. Belke DD, Betuing S, Tuttle MJ, et al. Insulin signaling coordinately regulates cardiac size, metabolism, and contractile protein isoform expression. J Clin Invest 2002;109:629–39.
79. Hu P, Zhang D, Swenson L, Chakrabarti G, Abel ED, Litwin SE. Minimally invasive aortic banding in mice: effects of altered cardiomyocyte insulin signaling during pressure overload. Am J Physiol Heart Circ Physiol 2003;285:H1261–9.
80. Belke DD, Larsen TS, Gibbs EM, Severson DL. Altered metabolism causes cardiac dysfunction in perfused hearts from diabetic (db/db) mice. Am J Physiol Endocrinol Metab 2000;279:E1104–13.
81. Buchanan J, Mazumder PK, Hu P, et al. Reduced cardiac efficiency and altered substrate metabolism precedes the onset of hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity. Endocrinology 2005;146:5341–9.
82. Semeniuk LM, Kryski AJ, Severson DL. Echocardiographic assessment of cardiac function in diabetic db/db and transgenic db/db-hGLUT4 mice. Am J Physiol Heart Circ Physiol 2002;283: H976–82.
83. Chiu HC, Kovacs A, Blanton RM, et al. Transgenic expression of fatty acid transport protein 1 in the heart causes lipotoxic cardiomyopathy. Circ Res 2005;96:225–33.
84. Liao R, Jain M, Cui L, et al. Cardiac-specific overexpression of GLUT1 prevents the development of heart failure attributable to pressure overload in mice. Circulation 2002;106:2125–31.
85. Tian R, Abel ED. Responses of GLUT4-deficient hearts to ischemia underscore the importance of glycolysis. Circulation 2001;103:2961–6.
86. Mazumder PK, O'Neill BT, Roberts MW, et al. Impaired cardiac efficiency and increased fatty acid oxidation in insulin-resistant ob/ob mouse hearts. Diabetes 2004;53:2366–74.
87. Davidoff AJ, Mason MM, Davidson MB, et al. Sucrose-induced cardiomyocyte dysfunction is both preventable and reversible with clinically relevant treatments. Am J Physiol Endocrinol Metab 2004;286:E718–24.
88. Dutta K, Podolin DA, Davidson MB, Davidoff AJ. Cardiomyocyte dysfunction in sucrose-fed rats is associated with insulin resistance. Diabetes 2001;50:1186–92.
89. Ren J, Dominguez LJ, Sowers JR, Davidoff AJ. Troglitazone attenuates high-glucose-induced abnormalities in relaxation and intracellular calcium in rat ventricular myocytes. Diabetes 1996;45:1822–5.
90. Ren J, Dominguez LJ, Sowers JR, Davidoff AJ. Metformin but not glyburide prevents high glucose-induced abnormalities in relaxation and intracellular Ca2+ transients in adult rat ventricular myocytes. Diabetes 1999;48:2059–65.

91. Bozkurt B, Kribbs SB, Clubb FJ Jr., et al. Pathophysiologically relevant concentrations of tumor necrosis factor-alpha promote progressive left ventricular dysfunction and remodeling in rats. Circulation 1998;97:1382–91.
92. Kubota T, McTiernan CF, Frye CS, et al. Dilated cardiomyopathy in transgenic mice with cardiac-specific overexpression of tumor necrosis factor-alpha. Circ Res 1997;81:627–35.
93. Yang LL, Gros R, Kabir MG, et al. Conditional cardiac overexpression of endothelin-1 induces inflammation and dilated cardiomyopathy in mice. Circulation 2004;109:255–61.
94. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation 2003;107:3133–40.
95. Kalra PR, Moon JC, Coats AJ. Do results of the ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure) study spell the end for non-selective endothelin antagonism in heart failure? Int J Cardiol 2002;85:195–7.
96. Itoh H, Doi K, Tanaka T, et al. Hypertension and insulin resistance: role of peroxisome proliferator-activated receptor gamma. Clin Exp Pharmacol Physiol 1999;26:558–60.
97. Winkler G, Lakatos P, Salamon F, et al. Elevated serum TNF-alpha level as a link between endothelial dysfunction and insulin resistance in normotensive obese patients. Diabet Med 1999;16:207–11.
98. Cai L, Kang YJ. Oxidative stress and diabetic cardiomyopathy: a brief review. Cardiovasc Toxicol 2001;1:181–93.
99. Wang J, Song Y, Elsherif L, et al. Cardiac metallothionein induction plays the major role in the prevention of diabetic cardiomyopathy by zinc supplementation. Circulation 2006;113:544–54.
100. Galderisi M. Diastolic dysfunction and diabetic cardiomyopathy: evaluation by Doppler echocardiography. J Am Coll Cardiol 2006;48:1548–51.
101. Pop-Busui R, Kirkwood I, Schmid H, et al. Sympathetic dysfunction in type 1 diabetes: association with impaired myocardial blood flow reserve and diastolic dysfunction. J Am Coll Cardiol 2004;44:2368–74.
102. Quinones MJ, Hernandez-Pampaloni M, Schelbert H, et al. Coronary vasomotor abnormalities in insulin-resistant individuals. Ann Intern Med 2004;140:700–8.
103. Lager I. The insulin-antagonistic effect of the counterregulatory hormones. J Intern Med Suppl 1991;735:41–7.
104. Nikolaidis LA, Elahi D, Hentosz T, et al. Recombinant glucagon-like peptide-1 increases myocardial glucose uptake and improves left ventricular performance in conscious dogs with pacing-induced dilated cardiomyopathy. Circulation 2004;110:955–61.
105. Frustaci A, Kajstura J, Chimenti C, et al. Myocardial cell death in human diabetes. Circ Res 2000;87:1123–32.
106. Liggett SB, Tepe NM, Lorenz JN, et al. Early and delayed consequences of beta(2)-adrenergic receptor overexpression in mouse hearts: critical role for expression level. Circulation 2000;101:1707–14.
107. Nonogaki K. New insights into sympathetic regulation of glucose and fat metabolism. Diabetologia 2000;43:533–49.
108. Downing SE, Lee JC. Effects of insulin on experimental catecholamine cardiomyopathy. Am J Pathol 1978;93:339–52.
109. Wallhaus TR, Taylor M, DeGrado TR, et al. Myocardial free fatty acid and glucose use after carvedilol treatment in patients with congestive heart failure. Circulation 2001;103:2441–6.
110. Morisco C, Condorelli G, Trimarco V, et al. Akt mediates the cross-talk between beta-adrenergic and insulin receptors in neonatal cardiomyocytes. Circ Res 2005;96:180–8.
111. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403.
112. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343–50.
113. Wannamethee SG, Shaper AG, Perry IJ. Smoking as a modifiable risk factor for type 2 diabetes in middle-aged men. Diabetes Care 2001;24:1590–5.
114. Kemppainen J, Tsuchida H, Stolen K, et al. Insulin signalling and resistance in patients with chronic heart failure. J Physiol 2003;550:305–15.
115. Freeman DJ, Norrie J, Sattar N, et al. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. Circulation 2001;103:357–62.
116. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet 2003;362:759–66.
117. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000;342:145–53.
118. Bakris GL, Fonseca V, Katholi RE, et al. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. JAMA 2004;292:2227–36.
119. Jacob S, Rett K, Wicklmayr M, Agrawal B, Augustin HJ, Dietze GJ. Differential effect of chronic treatment with two beta-blocking agents on insulin sensitivity: the carvedilol-metoprolol study. J Hypertens 1996;14:489–94.
120. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. Lancet 2003;362:7–13.
121. Aussedat J, Ray A, Kay L, Verdys M, Harpey C, Rossi A. Improvement of long-term preservation of isolated arrested rat heart: beneficial effect of the antiischemic agent trimetazidine. J Cardiovasc Pharmacol 1993;21:128–35.
122. Fragasso G, Palloshi A, Puccetti P, et al. A randomized clinical trial of trimetazidine, a partial free fatty acid oxidation inhibitor, in patients with heart failure. J Am Coll Cardiol 2006;48:992–8.
123. Lee L, Campbell R, Scheuermann-Freestone M, et al. Metabolic modulation with perhexiline in chronic heart failure: a randomized, controlled trial of short-term use of a novel treatment. Circulation 2005;112:3280–8.
124. McCormack JG, Barr RL, Wolff AA, Lopaschuk GD. Ranolazine stimulates glucose oxidation in normoxic, ischemic, and reperfused ischemic rat hearts. Circulation 1996;93:135–42.
125. Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, et al. Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. JAMA 2007;297:1775–83.
126. Broderick TL, Quinney HA, Barker CC, Lopaschuk GD. Beneficial effect of carnitine on mechanical recovery of rat hearts reperfused after a transient period of global ischemia is accompanied by a stimulation of glucose oxidation. Circulation 1993;87:972–81.
127. Cevese A, Schena F, Cerotti G. Short-term hemodynamic effects of intravenous propionyl-l-carnitine in anesthetized dogs. Cardiologia 1989;34:95–101.
128. Ferrari R, Merli E, Cicchitelli G, Mele D, Fucili A, Ceconi C. Therapeutic effects of L-carnitine and propionyl-L-carnitine on cardiovascular diseases: a review. Ann N Y Acad Sci 2004;1033:79–91.
129. Gilde AJ, van der Lee KA, Willemsen PH, et al. Peroxisome proliferator-activated receptor (PPAR) alpha and PPARbeta/delta, but not PPARgamma, modulate the expression of genes involved in cardiac lipid metabolism. Circ Res 2003;92:518–24.
130. Guan Y, Hao C, Cha DR, et al. Thiazolidinediones expand body fluid volume through PPARgamma stimulation of ENaC-mediated renal salt absorption. Nat Med 2005;11:861–6.
131. Nesto RW, Bell D, Bonow RO, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. October 7, 2003. Circulation 2003;108:2941–8.
132. Rosiglitazone: seeking a balanced perspective. Lancet 2007;369:1834.
133. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes—an interim analysis. N Engl J Med 2007;357:28–38.
134. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457–71.
135. Salehi M, D'Alessio DA. New therapies for type 2 diabetes based on glucagon-like peptide 1. Cleve Clin J Med 2006;73:382–9.