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, predicates 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.

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).
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 (VO₂max) 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).

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 consumes 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 and 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).
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 response to an insult—which contributes to HF and the vicious cycle of neurohormonal activation, serving to potentiate 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 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).

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).
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

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

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

CM = cardiomyopathy; FFA = free fatty acid; GLUT = glucose transporter; IRCM = insulin-resistant cardiomyopathy; LV = left ventricular; PPAR = peroxisome proliferator-activated receptor; TG = triglycerides.
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, VO_{2max} 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).

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**Table 2 Potential Treatments for Insulin-Resistant Cardiomyopathy**

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

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 principal 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 pharmacologic 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...
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.

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REFERENCES


Osorio JC, Stanley WC, Linke A, et al. Impaired myocardial fatty
Nikolaidis LA, Poornima I, Parikh P, Magovern M, Shen YT,
Jagasia D, Whiting JM, Concato J, Pfau S, McNulty PH. Effect of
Iozzo P, Chareonthaitawee P, Dutka D, Betteridge DJ, Ferrannini E,
Neitzel AS, Carley AN, Severson DL. Chylomicron and palmitate
Razeghi P, Young ME, Alcorn JL, Moravec CS, Frazier OH,
Christoffersen C, Bollano E, Lindegaard ML, et al. Cardiac lipid
Chiu HC, Kovacs A, Ford DA, et al. A novel mouse model of
Finck BN, Han X, Courtois M, et al. A critical role for PPARalpha-
Calvani M, Reda E, Arrigoni-Martelli E. Regulation by carnitine
Morrow DA, Givertz MM. Modulation of myocardial energetics:
Taanman H, Van Der Laarse A, Aronson J, et al. Reduced expression of
Vinkman D, Whiting JM, Concato J, Pfau S, McNulty PH. Effect of
Nikolaides LA, Poomima I, Parikh P, Magovern M, Shen YT,
in the control of myocardial uncoupling protein levels. Diabetes
47. Opie LH. The metabolic vicious cycle in heart failure. Lancet
45. Christoffersen C, Bollano E, Lindegaard ML, et al. Cardiac lipid
44. Christoffersen C, Bollano E, Lindegaard ML, et al. Cardiac lipid
43. Christoffersen C, Bollano E, Lindegaard ML, et al. Cardiac lipid
42. Finck BN, Han X, Courtois M, et al. A critical role for PPARalpha-
41. Osorio JC, Stanley WC, Linke A, et al. Impaired myocardial fatty
68. Nikolaidis LA, Poornima I, Parikh P, Magovern M, Shen YT,
67. Jagasia D, Whiting JM, Concato J, Pfau S, McNulty PH. Effect of
66. Iozzo P, Chareonthaitawee P, Dutka D, Betteridge DJ, Ferrannini E,
65. Finck BN, Lehman JJ, Leone TC, et al. The cardiac phenotype
59. Razeghi P, Young ME, Alcorn JL, Moravec CS, Frazier OH,
58. Nikolaidis LA, Poornima I, Parikh P, Magovern M, Shen YT,
57. Morrow DA, Givertz MM. Modulation of myocardial energetics:
56. Finck BN, Lehman JJ, Leone TC, et al. The cardiac phenotype
55. Razeghi P, Young ME, Alcorn JL, Moravec CS, Frazier OH,


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.


