Insulin Resistance in Dilated Cardiomyopathy

Ankur Shah, MD, Richard P. Shannon, MD

Cardiovascular Research Institute and Department of Medicine, Allegheny General Hospital, Pittsburgh, PA

The recognition that insulin resistance is an accompaniment to advanced dilated cardiomyopathy is a relatively recent revelation, but the consequences may be considerable for the failing heart. The failing heart develops a dependence on glucose as its preferred metabolic substrate, given the efficiency of glucose oxidation in the generation of high-energy phosphates. The increased preference for glucose oxidation requires that glucose transport and oxidation be highly regulated. Myocardial insulin resistance in advanced dilated cardiomyopathy limits both glucose uptake and oxidation and impairs the heart's ability to generate much needed adenosine triphosphate. We provide evidence of insulin resistance in dilated cardiomyopathy and explore the relationship to increased sympathetic nervous system activation, lipolysis, and the subsequent alteration in the insulin signaling cascade. Together, these data provide a growing rationale for the development of clinical strategies to overcome insulin resistance in dilated cardiomyopathy.
[Rev Cardiovasc Med. *2003;4(suppl 6):S50–S57*]

Key words: Insulin resistance • Nonesterified fatty acids • Lipolysis • Sympathetic nervous system activation • Insulin signaling

Insulin resistance is defined as impaired metabolic, mitogenic, and vascular effects of the hormone. The term is used classically to refer to impaired insulin-mediated glucose uptake in skeletal muscle and adipose tissue. Insulin resistance is being recognized with increasing frequency as a potent contributor to cardiovascular risk.[1,2] This is due to the now well-recognized fact that insulin resistance presages the development of type 2 diabetes by many years

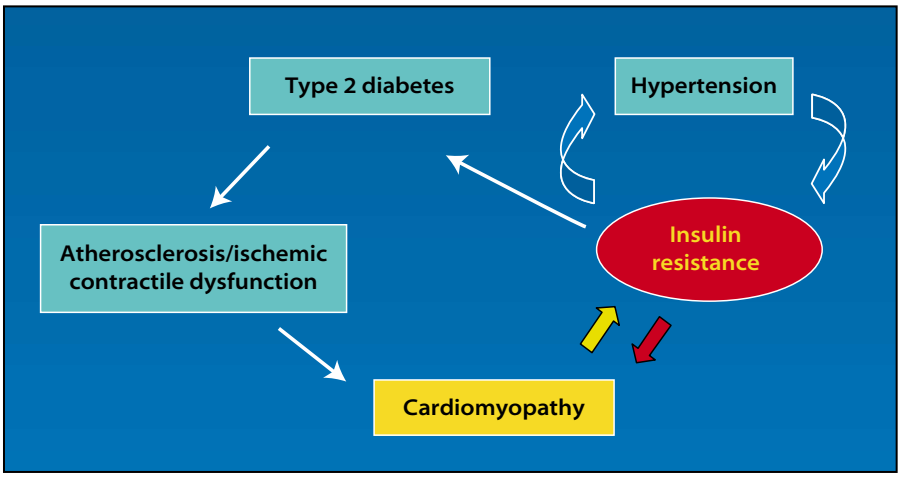

Figure 1. *Insulin resistance is central in the pathogenesis of both type 2 diabetes and cardiovascular disorders, including hypertension and atherosclerosis. Although insulin resistance can lead indirectly to the development of cardiomyopathy, it is now recognized that cardiomyopathy can lead to the development of insulin resistance at both a whole body and a myocardial level. Myocardial insulin resistance has important implications for the failing heart, with its preference for glucose oxidation.*

and is central in its pathogenesis. In addition, the increasing recognition of the principal role that insulin resistance plays in the metabolic syndrome has served to highlight its importance in the pathogenesis of cardiovascular disease.[3]

It is generally considered that insulin resistance and type 2 diabetes predispose to cardiovascular disease by enhancing atherosclerosis (Figure 1).[1–3] Coronary atherosclerosis in turn contributes to ischemic injury that leads to ischemic cardiomyopathy over time. Type 2 diabetes, hyperinsulinemia, glucotoxicity, and lipotoxicity are thought to directly impair myocardial contractility and alter myocardial ultrastructure, although the evidence of a causative role is less clear than in the pathogenesis of atherosclerosis. Myocardial contractile dysfunction and ventricular remodeling are the hallmarks of dilated cardiomyopathy and are typically considered to be remote consequences of the cumulative insults of diabetes over many years.[1] However, recent clinical evidence suggests that the development of myocardial contractile dysfunction and dilated cardiomyopathy may trigger insulin resistance at both the whole body and myocardial levels. The development of myocardial insulin resistance in dilated cardiomyopathy has potential significant consequences, given the preference of the failing heart for glucose as its metabolic substrate. In this article, we review the evidence that dilated cardiomyopathy is associated with the development of whole body and myocardial insulin resistance and the consequences for substrate utilization of the failing heart. We also review alterations in myocardial insulin signaling as potential targets for therapeutic intervention. We establish the role of increased sympathetic nervous system activation and associated lipolysis in the pathogenesis of myocardial insulin resistance. Finally, we discuss the implications for overcoming insulin resistance in preventing the progression of dilated cardiomyopathy to end-stage heart failure.

Myocardial Substrate Preference in the Failing Heart

The heart is unique among organ systems in its continuous need for high-energy phosphates to maintain contractile function and thereby provide oxygenated blood to other organ systems to meet their metabolic needs.[4] The continuous requirement for high-energy phosphates imposes a significant metabolic burden on the heart to generate adenosine triphosphate (ATP) from the complete oxidation of available metabolic substrates. The heart possesses a limited ability to store substrate, particularly fatty acids, for oxidative phosphorylation. Therefore, the heart has a continuous requirement for transporting as well as oxidizing available substrate.

Under normal physiologic circumstances, the heart possesses the ability to use numerous substrates for the generation of high-energy phosphates, including nonesterified fatty acids (NEFA), glucose, and lactate.[5,6] The choice of substrate is based on substrate availability, hormonal milieu, oxygen availability, and metabolic demands. In the normal adult heart, NEFA are the preferred metabolic substrate because of the high yield of ATP when NEFA are fully oxidized. However, under circumstances of increased myocardial work or limited oxygen availability, the heart turns to glucose as the more efficient fuel for ATP generation. When the heart is injured and left ventricular (LV) function is depressed on a chronic basis, there is a shift to glucose as the preferred substrate under basal circumstances. Work of Taegtmeyer and colleagues[4,7] has now demonstrated that this shift in substrate preference is a highly regulated transcriptional event. Importantly, the changes in gene transcription involve down-regulation of transport mechanisms and enzymes involved in fatty acid oxidation. This includes decreases in the NEFA

receptor—peroxisome proliferator activated receptor-α (PPARα])—and its co-factor, the retinoic acid receptor RXR, as well as a series of enzymes, including carnitine palmitoyltransferase-1 (CPT-1), which is rate limiting in the transport of fatty acid coenzyme A (CoA) to the inner mitochondrial membrane.[4,8,9] These events recapitulate the fetal gene profile of the heart, as has been seen with many other genetic programs following cardiac injury.[7] The functional consequence of this genetic reprogramming is an increased reliance of the failing heart on the transport and oxidation of glucose.

There is a requirement for adequate insulin availability and action to efficiently transport and oxidize glucose. The requirement becomes more pressing as the failing heart's dependence on glucose grows.

Myocardial glucose metabolism has been studied extensively in normal and diseased myocardium. There is a requirement for insulin to efficiently transport glucose across the sarcolemmal membrane using a highly specific transporter, glucose transporter-4 (GLUT-4).[4] Although an alternative, non–insulin-dependent mechanism does exist in the GLUT-1 transporter, its abundance and significance is pale in comparison to the GLUT-4 transporter. Insulin is also essential in activating key rate-limiting steps in glycolysis (Akt-1–dependent phosphorylation of phosphofructokinase). Thus, there is a requirement for adequate insulin availability and action to efficiently transport and oxidize glucose. The requirement becomes more pressing as the failing heart's dependence on glucose grows.

Clinical Evidence in Congestive Heart Failure

There is a considerable body of literature that supports the concept that LV dysfunction predisposes to the development of whole body insulin resistance in humans.

Amato and colleagues[10] studied the extent to which congestive heart failure (CHF) promoted insulin resistance as the major pathophysiologic risk for diabetes mellitus. In 1339 elderly subjects, the investigators determined that CHF predicted insulin-dependent diabetes mellitus (IDDM) independently of age, sex, family history, body mass index, waist:hip ratio, blood pressure, and therapy for CHF. Suskin and associates[11] observed glucose abnormalities in 43% of patients with CHF and correlated these findings with the New York Heart Association classification of symptoms. Paolisso and coworkers[12,13] demonstrated that insulin-mediated glucose uptake is an independent prognostic factor in heart failure. Several studies demonstrated fasting hyperinsulinemia and various degrees of insulin resistance using minimal modeling of glucose disposition, euglycemic-hyperinsulinemic clamps or positron emission tomography (PET) scanning in patients with heart failure.[14–17] However, the mechanisms and the time course of the development of insulin resistance have not been explored in humans with dilated cardiomyopathy nor has there been an attempt to discriminate whole body insulin resistance from myocardial insulin resistance in LV dysfunction. Data in patients with coronary disease[18] and cardiac hypertrophy[19] have suggested that there is comparable myocardial and whole body insulin resistance, despite normal fasting insulin levels. However, myocardial glucose disposition and coronary blood flow were inferred from positron emission tomography measurements in these studies without direct assessments of either transmyocardial glucose measurements or coronary blood flow. Surprisingly, Jagasia and colleagues[20] found no evidence of myocardial insulin resistance in type 2 diabetics with coronary artery disease when transmyocardial glucose measurements and direct measurements of coronary blood flow were used, despite significant impairment in whole body glucose uptake. Importantly, all patients had normal LV ejection fractions (> 45%). Intracoronary infusion of insulin to patients with type 2 diabetes with normal LV function revealed intact myocardial glucose uptake and glucose oxidation, despite significant impairment of both cellular processes in skeletal muscle. In contrast, coronary vascular responses to intracoronary hyperinsulinemia were impaired in type 2 diabetics compared with nondiabetic subjects.

These data suggest that there is a discrepancy between myocardial insulin action and coronary vascular responses to insulin in type 2 diabetes. The extent to which these differences are attributable to organ-specific insulin action or the associated effects of hyperglycemia is unknown. Furthermore, vascular insulin resistance explains the impairment in coronary flow reserve documented in IDDM in the absence of epicardial atherosclerosis.[21]

A major limitation of these studies has been failure to consider the role of elevated free fatty acids in the observed insulin resistance. Physiologic increases in NEFA can contribute importantly to insulin resistance by decreasing insulin-stimulated glucose uptake and decreasing glycogen synthase activi-

ty. The mechanism whereby NEFA impairs glucose uptake involves impaired translocation of GLUT-4.[22,23] Furthermore, there is little data to determine whether insulin resistance contributes to LV dysfunction or coronary vascular abnormalities in dilated cardiomyopathy or whether ameliorating myocardial insulin sensitivity improves LV function. Finally, there are few data on the cellular signaling abnormalities that accompany myocardial insulin resistance in these human studies and whether they differ from those described in skeletal muscle.

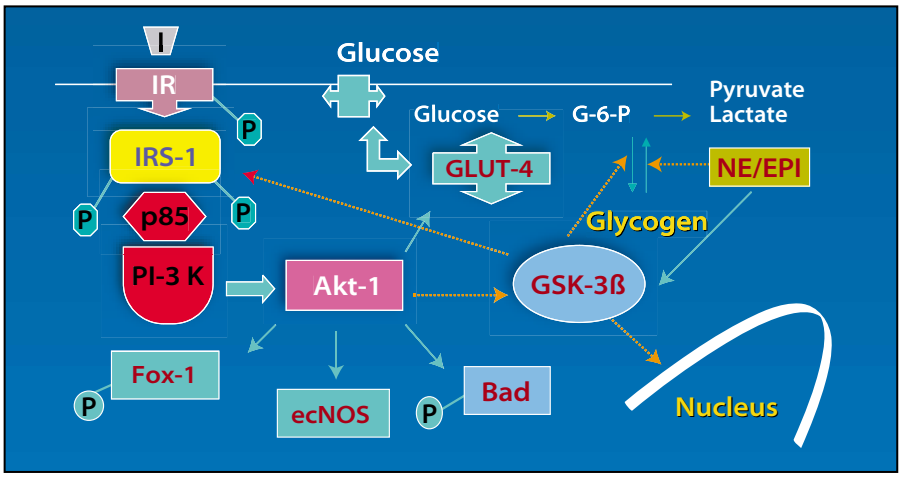

Figure 2. *The cellular steps in the insulin (I) signaling cascade, underscoring the metabolic actions of insulin as well as its effects on growth and survival. The serine/threonine kinase Akt-1 is the central mediator of these actions of insulin. ecNOS, endothelial nitric oxide synthase; G-6-P, glucose-6-phosphate; GLUT-4, glucose transporter-4; GSK-3ß, glycogen synthase kinase-3ß; IR, insulin receptor; IRS-1, insulin receptor substrate-1; NE/EPI, norepinephrine/epinephrine; P, phosphorylation site; PI-3 K, phosphatidylinositol-3 kinase.*

Insulin Signaling Cascade in the Heart

From a metabolic perspective, the principal action of insulin is to facilitate the translocation of the insulin-sensitive GLUT-4 transporter from the cytosol to the plasma membrane. The steps involved in effecting these cellular actions of insulin are well understood in skeletal muscle and adipose tissue. Much of this work has been done employing in vitro cell culture models. A schematic illustration of the insulin signaling cascade is illustrated in Figure 2. Insulin binds to membrane-bound insulin receptors (IR) that act as tyrosine kinases to autophosphorylate regulatory subunits (IR-ß) on the receptor. The activated tyrosine kinase also phosphorylates a key docking protein, insulin receptor substrate-1 (IRS-1), at key tyrosine residues. The phosphorylation of IRS-1 facilitates the recruitment of phosphatidylinositol-3 (PI-3) kinase to the plasma membrane. Activation and recruitment of PI-3 kinase is the rate-limiting step in the cellular insulin signaling cascade. PI-3 kinase generates tris phosphatidylinositides (PtInds 3' 4' 5'*P*) in the lipid membrane that are essential to the activation of the central cellular mediator of insulin action, protein kinase B, or Akt-1. Akt-1 is a highly conserved serine/threonine kinase with pleomorphic cellular actions.[24,25] Akt-1 was first identified as a proto-oncogene that conferred immortality on cancer cell lines. It has been implicated widely in a number of cardiovascular pathophysiologic conditions, including myocardial growth through the inhibition of glycogen synthase kinase-3ß (GSK-3ß). GSK-3ß phosphorylates a key nuclear transcription factor (NFAT-3) implicated in the pathogenesis of myocardial hypertrophy. Inhibition of GSK-3ß by activated Akt-1 allows NFAT-3 to translocate to the nucleus and activate a series of growth programs mediated by the transcription factor GATA-4. Akt-1 activation also facilitates cardiomyocyte survival through the activation of the anti-apoptotic pathways involving Bcl-2.[25] Akt-1 activation also enhances the activity of nitric oxide synthase isoform (NOS3), thereby facilitating the production of nitric oxide and ameliorating endothelial dysfunction.[24]

Akt-1 acts as a central intracellular mediator of insulin action, governing glucose homeostasis by facilitating intracellular transport of substrate as well as its oxidative and nonoxidative metabolism through actions on glycolytic and glycogen synthesis pathways, respectively.

However, Akt-1 plays a fundamental role in glucose homeostasis in the heart as well as other insulin-sensitive tissues.[25] Akt-1 activation is essential for the efficient translocation of the GLUT-4 transporter as well as the activation of the forkhead family of nuclear transcription factors that induce key glucoregulatory enzymes. Akt-1 phosphorylation and resultant inhibition of GSK-3ß results in the activation of glycogen synthase, facilitating the nonoxidative metabolism of glucose to glycogen under appropriate circumstances. Finally, Akt-1 activation results in the phosphorylation of phosphofructo-

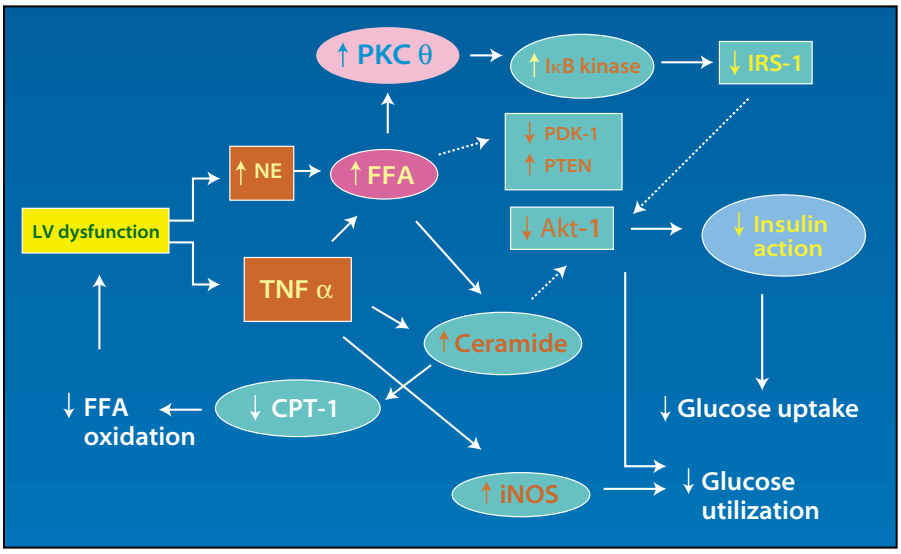

Figure 3. *The role of the sympathetic nervous system as a trigger and nonesterified fatty acids (NEFA) as a mediator of altered insulin signaling in dilated cardiomyopathy. The illustration underscores the central role of NEFA in altering insulin signaling through three cellular mechanisms: atypical protein kinase C (PKC Θ), induction of phosphatases (PTEN [phosphatidylinositol phosphate 3'-phosphatase]), and induction of ceramide. These cellular events constitute potential therapeutic targets for restoring insulin signaling. CPT-1, carnitine palmitoyltransferase-1; FFA, free fatty acids; iNOS, inducible nitric oxide synthase; IRS-1, insulin receptor substrate-1; LV, left ventricular; NE, norepinephrine; PDK-1, phosphatidylinositide-dependent kinase-1; TNFα, tumor necrosis factor-α.*

kinase-1 at two key regulatory sites, facilitating the activity of this rate-limiting enzyme in glycolysis.[24,25] Thus, Akt-1 acts as a central intracellular mediator of insulin action, governing glucose homeostasis by facilitating intracellular transport of substrate as well as its oxidative and nonoxidative metabolism through actions on glycolytic and glycogen synthesis pathways, respectively.

The complete activation of Akt-1 is dependent on the phosphorylation of two key sites and is governed by two distinct kinases. Phosphatidylinositide-dependent kinase-1 (PDK-1) phosphorylates Akt-1 at a key threonine residue (Thr 308) located in the catalytic domain of Akt-1. Integrin-linked kinase-2 (ILK-2) phosphorylates Akt-1 at a key serine residue (Ser 473) located in the regulatory unit of the kinase.[24,25] These two kinases are themselves dependent on the generation of tris phosphatidylinositides in the plasma membrane. Failure to generate tris phosphatidylinositides through activation of PI-3 kinase or degradation by phosphatases impairs the activation of Akt-1.

Increased Sympathetic Nervous System Activation: A Potential Trigger to Myocardial Insulin Resistance in Dilated Cardiomyopathy

Figure 3 provides a conceptual framework by which LV dysfunction and the resultant dilated cardiomyopathy might lead to the development of myocardial insulin resistance. The myocardium is among the most richly innervated organs by the sympathetic nervous system (SNS), given the need to adjust performance on a moment-to-moment basis, depending on demand from other organ systems. It is well established that LV dysfunction leads to the activation of the SNS and the release of norepinephrine from presynaptic nerve terminals. The acute response is designed to maintain ventricular performance and cardiac output at or near normal. It is accompanied by increased peripheral sympathetic activation designed to maintain organ perfusion through regional vasoconstriction and diversion of oxygenated blood to vital organs. Although this response is essential in preserving organ perfusion acutely, the tonic activation of the SNS leads to adverse cardiovascular conditions. These include increased myocardial oxygen consumption associated with sympathetically mediated increases in heart rate and contractility through ß1-adrenergic receptors and increased ventricular load imposed by increased peripheral vasoconstriction mediated by vascular α1-adrenergic receptors. As such, chronic activation of the SNS in dilated cardiomyopathy leads to increased consumption of high-energy phosphates, further imposing on the already-stressed metabolic circumstances of the failing heart. In support of these chronic adverse effects of SNS activation is a plethora of clinical and experimental evidence that inhibition of the SNS through the use of adrenergic receptor antagonists improves clinical outcomes and mortality in patients with dilated cardiomyopathy.

In support of these chronic adverse effects of SNS activation is a plethora of clinical and experimental evidence that inhibition of the SNS through the use of adrenergic receptor antagonists improves clinical outcomes and mortality in patients with dilated cardiomyopathy.

In addition to the aforemen-

tioned adverse hemodynamic effects of chronic SNS activation, catecholamines are known to be potent counterregulatory hormones to the action of insulin.[26,27] Among the effects are the potent actions of catecholamines, particularly norepinephrine, to induce lipolysis and increase circulating NEFA.[27] The increase in circulating NEFA may play a central role in mediating myocardial insulin resistance.

In addition, glucagon, a potent counterregulatory hormone to the action of insulin, mediates its myocardial effects through the activation of ß2-adrenergic receptors. A critical consequence of this action is to increase plasma glucose levels by stimulating glycogenolysis during periods of hypoglycemia. In addition, glucagon facilitates NEFA oxidation by decreasing malonyl CoA, a potent inhibitor of lipid oxidation. Finally, glucagon decreases phospho-2, 6 bisphosphate, impairing the activation of phosphofructokinase and inhibiting glycolysis. In this regard, it is important to note that combined SNS antagonism with carvedilol improves myocardial glucose uptake in patients with dilated cardiomyopathy.[28]

Taken together, these data suggest that chronic SNS activation in dilated cardiomyopathy may play an important pathophysiologic role in triggering insulin resistance by increasing circulating levels of NEFA and altering the balance between glucose and NEFA oxidation in the failing heart. While blocking the SNS is associated with increased myocardial glucose uptake, the precise mechanisms of the beneficial effects remain to be elucidated.

NEFA: A Central Mediator of Myocardial Insulin Resistance in Dilated Cardiomyopathy

Despite the lack of general recognition, there is both clinical and experimental evidence to suggest that plasma levels of NEFA are increased in cardiomyopathy. NEFA are the product of lipolysis, in which triglycerides are converted to glycerol and NEFA. Circulating NEFA can be taken up by nonadipose tissue and oxidized to generate ATP. However, in cardiomyopathy, the enzymatic pathways for NEFA oxidation in the heart are down-regulated in a series of tightly regulated transcriptional events that begin with the PPARα receptor, its coreceptor, the retinoic acid receptor, and cofactor PCG-1.[8,9] In the absence of oxidation, NEFA may be stored in the form of triacylglycerol in nonadipose tissues, such as the heart. Stored NEFA in nonadipose tissue has now been implicated in mediating lipotoxicity.[8]

Chronic SNS activation in dilated cardiomyopathy may play an important pathophysiologic role in triggering insulin resistance by increasing circulating levels of NEFA and altering the balance between glucose and NEFA oxidation in the failing heart.

Fatty acid oxidation has long been implicated in the inhibition of glucose oxidation through the competitive generation of intermediary metabolites.[6] The generation of fatty acyl CoA directly inhibits the action of hexokinase, the first committed step in the glycolytic pathway. The conversion of fatty acyl CoA to acetyl CoA alters the mitochondrial ratio of acetyl CoA/CoA, which directly inhibits the pyruvate dehydrogenase complex and glucose oxidation. Finally, increased β-oxidation of acetyl CoA leads to increased efflux of citrate from the mitochondria to the cytosol, where it inhibits phosphofructokinase.

More recently, it has been recognized that NEFA can alter insulin signaling directly as opposed to competitively by interfering with several steps in the insulin-signaling cascade (Figure 3). Recent evidence has suggested that NEFA can lead to activation of atypical protein kinase (PKC θ).[29,30] In turn, these protein kinases activate IκB kinase, a serine kinase that can phosphorylate serine residues on the docking protein, IRS-1. Serine phosphorylation of IRS-1 inhibits the recruitment of PI-3 kinase, mitigating insulin signaling. An alternative mechanism involves the induction of the anti-oncogenic phosphatase and tensin homologue deleted on chromosome 10 (PTEN) by NEFA, mediating activation of PPARγ nuclear receptors. PTEN activation results in the dephosphorylation of tris phosphatidylinositide, impairing Akt-1 activation. A third mechanism whereby NEFA can impair insulin signaling involves the generation of the intracellular sphingolipid ceramide. Ceramide is known to induce protein phosphatase-2 (PP-2), which is involved in the deactivation of Akt-1. Importantly, these mechanisms,

Increased circulating NEFA appear to be a common feature of cardiomyopathy and may contribute importantly to altered glucose homeostasis and insulin action by both direct and indirect mechanisms.

although attractive, have not been demonstrated in myocardium.

Nonetheless, increased circulating NEFA appear to be a common feature of cardiomyopathy and may contribute importantly to altered glucose homeostasis and insulin action by both direct and indirect mechanisms. Whether altering increased plasma NEFA will restore myocardial insulin responsiveness remains to be elucidated.

Overcoming Insulin Resistance in Dilated Cardiomyopathy as a Mechanism for Clinical Improvement

Based on the existing clinical information and the theoretical constructs presented above, it is reasonable to assume that the failing heart, particularly the heart with advanced dilated cardiomyopathy, is poised on the brink of myocardial energy deprivation and might benefit from enhanced myocardial glucose uptake and oxidation. The data of Paolisso and colleagues[10,12,13] demonstrated evidence of both whole body and myocardial insulin resistance in patients with advanced dilated cardiomyopathy. What remains to be determined is whether overcoming myocardial insulin resistance and enhancing myocardial glucose uptake and oxidation will improve clinical and hemodynamic outcomes in heart failure. There is an extensive literature, both clinical and experimental, demonstrating that intensive insulin treatment in the setting of myocardial infarction[31,32] and cardiac surgery[33] is associated with improved clinical outcomes. However, the majority of these trials were conducted in diabetics, and the administration of insulin required as much as 2 liters of concomitant glucose infusion to mitigate hypoglycemia.[32] These volume requirements make conventional insulin therapy unattractive in heart failure, in which such an infusion would be contraindicated. Furthermore, insulin resistance in dilated cardiomyopathy is associated with high fasting insulin levels. Although pharmacologic insulin levels do improve glucose uptake, a more attractive strategy would involve insulin-sensitizing agents, such as the thiazolidine-

Although pharmacologic insulin levels do improve glucose uptake, a more attractive strategy would involve insulin-sensitizing agents, such as the thiazolidinediones.

Main Points

- The development of myocardial insulin resistance in dilated cardiomyopathy has potential significant consequences, given the preference of the failing heart for glucose as its metabolic substrate.
- The heart is unique among organ systems in its continuous need for high-energy phosphates to maintain contractile function and thereby provide oxygenated blood to other organ systems to meet their metabolic needs.
- There is a considerable body of literature that supports the concept that left ventricular dysfunction predisposes to the development of whole body insulin resistance in humans.
- From a metabolic perspective, the principal action of insulin is to facilitate the translocation of the insulin-sensitive GLUT-4 transporter from the cytosol to the plasma membrane.
- Akt-1 acts as a central intracellular mediator of insulin action, governing glucose homeostasis by facilitating intracellular transport of substrate as well as its oxidative and nonoxidative metabolism through actions on glycolytic and glycogen synthesis pathways, respectively.
- Combined sympathetic nervous system (SNS) antagonism with carvedilol improves myocardial glucose uptake in patients with dilated cardiomyopathy. Chronic SNS activation in dilated cardiomyopathy may play an important pathophysiologic role in triggering insulin resistance by increasing circulating levels of nonesterified fatty acids (NEFA) and altering the balance between glucose and NEFA oxidation in the failing heart.
- It is reasonable to assume that the failing heart, particularly the heart with advanced dilated cardiomyopathy, is poised on the brink of myocardial energy deprivation and might benefit from enhanced myocardial glucose uptake and oxidation.
- Recent clinical evidence suggests that the development of myocardial contractile dysfunction and dilated cardiomyopathy may trigger insulin resistance at both the whole body and myocardial levels.

diones (TZDs). At present, concerns about peripheral edema have limited the use of TZDs in patients with heart failure, although the mechanisms of this phenomenon have not been elucidated. An attractive alternative might involve the derivatives of the proglucagon family, the glucagon-like peptides, which possess insulinotropic, insulinomimetic, and glucagonostatic properties. Importantly, these naturally occurring incretins are largely devoid of hypoglycemic risks, as their insulinotropic properties are attenuated when plasma glucose falls below 70 mg/dL. The short duration of action requires continuous subcutaneous infusion, which constitutes a potential drawback to chronic treatment. Nonetheless, with our emerging understanding of the role of insulin resistance and the ever-increasing recognition of its potential deleterious consequences on the failing heart, additional experimental and clinical trials are warranted to determine whether myocardial insulin resistance will emerge as a new and important therapeutic target in heart failure. ■

References

1. Standl E, Schnell O. A new look at the heart in diabetes mellitus: from ailing to failing. *Diabetologia*. 2000;43:1455–1469.
2. Rubins HB, Robins SJ, Collins D, et al. Diabetes, plasma insulin and cardiovascular disease. Subgroup analysis from the Department of Veterans Affairs High-Density Lipoprotein Intervention Trial [VA-HIT]. *Arch Intern Med*. 2002;162:2597–2604.
3. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among U.S. adults. Findings from the Third National Health and Nutrition Examination Survey. *JAMA*. 2002; 287:356–359.
4. Taegtmeyer H. Switching metabolic genes to build a better heart. *Circulation*. 2002; 106:2043–2045.
5. Taegtmeyer H, McNulty P, Young ME. Adaptation and maladaptation of the heart in diabetes: part I. general concepts. *Circulation*. 2002;105:1727–1733.
6. Young ME, McNulty P, Taegtmeyer H. Adaptation and maladaptation of the heart in diabetes: part II. potential mechanisms. *Circulation*. 2002;105:1861–1870.
7. Razeghi P, Young ME, Alcorn JL, et al. Metabolic gene expression in fetal and failing human heart. *Circulation*. 2001;104:2923–2931.
8. 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;106:606–612.
9. Davilia-Roman VG, Vedala G, Herrero P, et al. Altered myocardial fatty acid and glucose metabolism in idiopathic dilated cardiomyopathy. *J Am Coll Cardiol*. 2002;40:271–277.
10. 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;23:213–218.
11. 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;21:1368–1375.
12. Paolisso G, De Riu S, Marrazzo G, et al. Insulin resistance and hyperinsulinemia in patients with chronic congestive heart failure. *Metabolism*. 1991;40:972–977.
13. 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; 83:1338–1344.
14. Coats AJ, Anker S. Insulin resistance in chronic heart failure. *J Cardiovasc Pharmacol*. 2000;35(7 suppl 4):S9–S14.
15. Swan JW, Walton C, Godsland IF, et al. Insulin resistance in chronic heart failure. *Eur Heart J*. 1994;15:1528–1532.
16. 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;30:527–532.
17. Doehner W, Anker SD, Coats AJ. Defects in insulin action in chronic heart failure. *Diabetes Obes Metab*. 2000;2:203–212.
18. Paternostro G, Camici PG, Lammerstma AA, et al. Cardiac and skeletal muscle insulin resistance in patients with coronary heart disease. A study with positron emission tomography. *J Clin Invest*. 1996;98:2094–2099.
19. Paternostro G, Pagano D, Gnecchi-Ruscone T, et al. Insulin resistance in patients with cardiac hypertrophy. *Cardiovasc Res*. 1999;42:246–253.
20. Jagasia D, Whiting JM, Concato J, et al. Effect of non-insulin-dependent diabetes mellitus on myocardial insulin responsiveness in patients with ischemic heart disease. *Circulation*. 2001; 103:1734–1739.
21. Pitkanen OP, Nuutila P, Raitakari OT, et al. Coronary flow reserve is reduced in young men with IDDM. *Diabetes*. 1998;47:248–254.
22. Battilana P, Seematter G, Schneiter P, et al. Effects of free fatty acids on insulin sensitivity and hemodynamics during mental stress. *J Clin Endocrinol Metab*. 2001;86:124–128.
23. Boden G. Free fatty acids—the link between obesity and insulin resistance. *Endocr Pract*. 2001;7:44–51.
24. Hemmings BA, Brazil DP. Ten years of protein kinase B signalling: a hard Akt to follow. *Trends Biochem Sci*. 2001;26:657–664.
25. Lawlor MA, Alessi DR. PKB/Akt: a key mediator of cell proliferation, survival and insulin responses. *J Cell Sci*. 2001;114:2903–2910.
26. Hjemdhal P. Stress and the metabolic syndrome, an interesting but enigmatic association. *Circulation*. 2002;106:2634–2636.
27. Nonogaki K. New insights into sympathetic regulation of glucose and fat metabolism. *Diabetologia*. 2000;43:533–549.
28. 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;103:2441–2446.
29. Kim JK, Kim YJ, Fillmore JF, et al. Prevention of fat-induced insulin resistance by salicylate. *J Clin Invest*. 2001;108:437–446.
30. Birnbaum MJ. Turning down insulin signaling. *J Clin Invest*. 2001;108:655–659.
31. Diaz R, Paolasso EA, Piegas LS, et al. Metabolic modulation of acute myocardial infarction. The ECLA [Estudios Cardiologicos Latinoamerica] Collaborative Group. *Circulation*. 1998;98: 2227–2234.
32. Malmberg K, Ryden L, Hamsten A, et al. Effects of insulin treatment on cause- specific one-year mortality and morbidity in diabetic patients with acute myocardial infarction. DIGAMI Study Group. Diabetes Insulin-Glucose in Acute Myocardial Infarction. *Eur Heart J*. 1996;17:1337–1344.
33. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med*. 2001;345:1359–1367.