Diabetic Cardiomyopathy: The Search for a Unifying Hypothesis

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Abstract—Although diabetes is recognized as a potent and prevalent risk factor for ischemic heart disease, less is known as to whether diabetes causes an altered cardiac phenotype independent of coronary atherosclerosis. Left ventricular systolic and diastolic dysfunction, left ventricular hypertrophy, and alterations in the coronary microcirculation have all been observed, although not consistently, in diabetic cardiomyopathy and are not fully explained by the cellular effects of hyperglycemia alone. The recent recognition that diabetes involves more than abnormal glucose homeostasis provides important new opportunities to examine and understand the impact of complex metabolic disturbances on cardiac structure and function. (Circ Res. 2006;98:596-605.)

Key Words: insulin resistance ■ diabetic cardiomyopathy ■ diastolic function ■ cardiac hypertrophy

The conventional wisdom holds that diabetes causes myocardial contractile dysfunction through accelerated atherosclerosis and hypertension. Much less appreciated and more controversial is the notion that diabetes mellitus affects cardiac structure and function, independent of blood pressure or coronary artery disease. Diabetic cardiomyopathy is a clinical condition, diagnosed when ventricular dysfunction develops in patients with diabetes in the absence of coronary atherosclerosis and hypertension.1-4 Despite the potential importance of this disease entity, the complex and multifactorial nature of the cellular and molecular perturbations that predispose to altered myocardial structure and function remain incompletely understood.

The epidemiological link between diabetes mellitus and the development of heart failure, independent of atherosclerotic cardiovascular disease, has been evident for the better part of three decades. The increased risk of heart failure persists in the diabetic patients after considering age, blood pressure, weight, cholesterol, as well as history of coronary artery disease.5,6 Notably, there is a significant association between diabetes and diastolic dysfunction leading to congestive heart failure in the absence of impaired systolic function.7,8 More recently, patients with unexplained idiopathic dilated cardiomyopathy were found to be 75% more likely to have diabetes than age matched controls.9 The association between diabetes and cardiomyopathy was strongest among individuals with microvascular complications of diabetes that parallels the duration and the severity of hyperglycemia. However, it has been difficult to ascertain from these epidemiological correlations the causal relationship between the commonly observed metabolic abnormalities and the specific cardiac phenotype. In this review, we provide an update of our current understanding of the complexities of diabetic cardiomyopathy with a special emphasis on the relationship between the metabolic abnormalities and cardiac dysfunction.
metabolic perturbations that accompany diabetes and the cellular consequences leading to altered myocardial structure and function.

### Cellular Mechanisms Predisposing to Diabetic Cardiomyopathy

The 3 characteristic metabolic disturbances evident in diabetic states are **hyperlipidemia** (usually in the form of increased triglycerides and nonesterified fatty acids [NEFAs]) and early **hyperinsulinemia** followed by pancreatic β-cell failure, leading eventually to **hyperglycemia**. Type 1 diabetes differs principally from type 2 diabetes in that it is unaccompanied by a period of hyperinsulinemia and is characterized by early- as opposed to late-onset hyperglycemia. Alterations in body mass (obesity) and adipocytokines (leptin, adiponectin) have also been implicated in the cardiovascular pathophysiology observed in diabetes. As such, the effects of increased NEFAs, altered insulin action, and hyperglycemia can be considered triggers to the cardiac phenotype in diabetes. An understanding of the cellular effects of these metabolic disturbances on cardiomyocytes should be useful in predicting the structural and functional cardiac consequences.

Extensive cellular and molecular studies have identified putative mediators, effectors, and intracellular targets of these metabolic triggers in the pathogenesis of cardiac dysfunction in diabetes (Figure 1). We review the cellular signaling pathways associated with these metabolic triggers that lead to altered myocardial structure and function.

### Increased NEFAs

NEFAs play a critical role in triggering the development of cellular insulin resistance but also have been implicated in the development of myocardial contractile dysfunction. NEFAs play a central role in altering cellular insulin signaling through several mechanisms leading to insulin resistance and compensatory hyperinsulinemia\(^{10–12}\) (Figure 2). In turn, hyperinsulinemia is an important trigger to the development of cardiac hypertrophy in diabetic cardiomyopathy (see below).

NEFAs activate the atypical protein kinase C (PKC) \(\theta\), a serine/threonine kinase that phosphorylates and subsequently activates IκB kinase. IκB kinase phosphorylates serine residues on insulin receptor substrate-1 (IRS-1), inhibiting its ability to bind SH2 domains of the p85 regulatory subunit of phosphatidylinositol 3-kinase (PI3K), impairing insulin signal transduction.\(^{12}\) Although this mechanism is active in skeletal muscle and adipose tissue, it has been less clear whether similar mechanisms are apparent in cardiac muscle.

Increases in intracellular NEFAs can also alter insulin signaling without affecting IRS-1/PI3K activation (Figure 2). Akt-1 activation is critically dependent on the generation of phosphatidylinositol 3,4,5-triphosphate (PtdIns(3,4,5)P\(_3\)) to bind the N-terminal pleckstrin domain and activate membrane bound kinases responsible for the phosphorylation of serine and threonine residues on Akt-1 that confer catalytic and regulatory properties.\(^{13–16}\) NEFAs are natural ligands for the nuclear receptor, peroxisome proliferator-activated receptor (PPAR) \(\gamma\), and can induce the upregulation of the phosphatase and tensin homolog deleted on chromosome 10 (PTEN) which dephosphorylates PtdIns(3,4,5)P\(_3\), preventing the activation of Akt-1.\(^{16}\)

NEFAs can directly alter myocardial contractility independent of altered insulin action by increasing NEFA flux into the myocardium.\(^{17}\) Recent evidence\(^{18}\) suggests that increases in fatty acyl coenzyme A (CoA) esters within cardiac myocytes may modulate the contractile state of the myocardium by opening of the \(\mathbf{K}_{\text{ATP}}\) channel. Activation of the \(\mathbf{K}_{\text{ATP}}\) channel leads to shortening of the action potential and
reduces transsarcolemmal calcium flux and subsequently myocardial contractility.

Finally, the increased intracellular accumulation of NEFAs may directly contribute to cell death under circumstances in which accumulating intracellular NEFAs do not undergo β oxidation. The reaction between palmityl-CoA, an intracellular intermediate of NEFAs, and serine leads to the generation of the sphingolipid ceramide, and this reaction may be facilitated by the cytokine, tumor necrosis factor (TNF) α. Ceramide can induce cellular apoptosis through the induction of nuclear factor κB, caspase 3 activation, and cytochrome c release and can inhibit DNA repair by blocking poly (ADP ribose) polymerase. Under these circumstances, increased NEFAs are said to cause lipotoxicity. Although lipotoxicity has been implicated in the reduction in pancreatic β-cell reserves, the relevance of these findings in the myocardium remain controversial.

Thus, NEFAs play a central role not only in inducing cellular insulin resistance but also in directly affecting myocardial contractility and, under specific circumstances, in the promotion of cardiomyocyte cell death.

**Hyperinsulinemia**

Cellular insulin resistance may presage frank diabetes by a decade or more and requires compensatory increases in plasma insulin levels to maintain glucose homeostasis in the face of impaired cellular insulin action, principally in skeletal muscle and liver. The nature and extent of the cellular insulin resistance may be selective to certain organ systems and may vary in terms of the metabolic, mitogenic, prosurvival, and vascular actions of insulin.

How then can hyperinsulinemia cause cardiac hypertrophy if the cellular actions of insulin are attenuated? The paradox is reconciled by the recognition that systemic hyperinsulinemia may accentuate cellular insulin action in insulin responsive tissues, such as the myocardium, that do not manifest cellular insulin resistance. In this regard, the mitogenic actions of insulin on myocardium during chronic systemic hyperinsulinemia bear directly the commonly observed finding of cardiac hypertrophy in diabetic cardiomyopathy.

There are at least 3 cellular mechanisms whereby hyperinsulinemia mediates cardiomyocyte hypertrophy (Figure 3). Acutely, insulin stimulates growth through the same PI3K/Akt-1 pathway by which it mediates glucose uptake. Akt-1 phosphorylates and inactivates glycogen synthases kinase-3 (GSK-3), a well-recognized inhibitor of nuclear transcription governing the hypertrophic process via the nuclear factor in activated lymphocytes (NFAT-3). In addition, Akt-1...
activates the mammalian target of rapamycin (mTOR) that activates the p70 ribosomal subunit 6 kinase-1, leading to increased protein synthesis.27–30 However, these mitogenic actions mediated through the insulin receptor may be mitigated when insulin signaling through the PI3K/Akt-1 pathway is impaired during chronic hyperinsulinemia.

However, chronic hyperinsulinemia may augment myocardial Akt-1 activation indirectly through increased sympathetic nervous system activation.26,31–33 Recent evidence suggests that chronic Akt-1 activation in cardiac myocytes is mediated through β2-adrenergic receptors via protein kinase A and Ca2+-calmodulin dependent kinase (CaMK),28 and these mechanisms may predominate when insulin signaling is attenuated through the PI3Kα pathway.

In addition, there are other insulin-mediated, but Akt-1–independent, pathways that may be operative, most notably the extracellular signal-regulated kinase (ERK)/mitogen-activated protein (MAP) kinase pathways.34,35 Significant cellular evidence exists for an insulin-induced activation of the p38 MAP kinase pathway,34 as well as prenylation of both Rho and Ras in the setting of hyperinsulinemia, leading to myocyte hypertrophy and expansion of the extracellular matrix (Figure 3). These redundant pathways provide a strong mechanistic basis for the development of cardiac hypertrophy associated with chronic hyperinsulinemia as an early accompaniment of type 2 diabetes, even though the glucoregulatory effects of insulin are attenuated.

Table 1 summarizes the effects of these alternative biochemical fates of glucose on cardiac structure and function in states of hyperglycemia.41–51 Taken together, these data provide mechanistic evidence linking hyperglycemia to altered expression and function of both the ryanodine receptor (RYR) and sarco(endoplasmonic reticulum Ca2+-ATPase (SERCA2) that may contribute to decreased systolic and diastolic function. In addition, hyperglycemia contributes to altered cardiac structure through posttranslational modification of the extracellular matrix.

### Cardiac Phenotypes in Experimental Models of Type 1 and Type 2 Diabetes Mellitus

The altered cardiac phenotypes associated with diabetic cardiomyopathy have been investigated in a wide array of experimental animal models.52,53 From a mechanistic perspective, the manifestations of diabetic cardiomyopathy should be predictable based on the duration and the severity of the abnormalities in NEFAs, insulin, and glucose homeostasis. However, the experimental conditions under which the models are studied add significant complexity to our understanding. In particular, the nature of the available substrates and hormonal milieu may be limited in isolated myocytes or isolated heart preparations and contribute to functional abnormalities that are not recapitulated in intact models. Table 2 summarizes the biochemical, structural, and functional abnormalities reported in these models.

### Hyperglycemia

The mechanism whereby hyperglycemia mediates tissue injury through the generation of reactive oxygen species has been elucidated largely through the work of the groups of Brownlee and colleagues.36–38 Hyperglycemia leads to increased glucose oxidation and mitochondrial generation of superoxide.37,39,40 In turn, excess superoxide leads to DNA damage and activation of poly (ADP ribose) polymerase (PARP) as a reparative enzyme.36 However, PARP also mediates the ribosylation and inhibition of glyceroldehyde phosphate dehydrogenase (GAPDH), diverting glucose from its glycolytic pathway and into alternative biochemical pathways that are considered the mediators of hyperglycemia induced cellular injury. These include increases in advanced glycation end products (AGEs), increased hexosamine and polyol flux, and activation of classical isoforms of protein kinase C. Table 1 serves as a compendium of the effects of hyperglycemia on cardiac structure and function in states of hyperglycemia.

### Models of Hyperglycemia Without Hyperinsulinemia

Streptozotocin (STZ) and alloxan are the 2 of the most common islet cell toxins that are used to induce type I diabetes in experimental animal models. The metabolic features include the prompt development of profound hyperglycemia (25 to 30 mmol/L), modest hypertriglyceridemia (200 to 400 μmol/L), ketosis, and markedly reduced plasma insulin levels (<20 pmol/L). As such, the model is particularly useful in examining the effects of hyperglycemia in the absence of hyperinsulinemia.

STZ- and alloxan-induced diabetes have been associated with myocardial atrophy as opposed to hypertrophy.54,55 This is associated with loss of contractile proteins, myocyte dropout without reparative fibrosis,56 consistent with the
absence of the mitogenic and prosurvival effects of insulin. Decreases in cardiac mass have also been noted with cardiac specific knockout of the insulin receptor associated with ventricular dilatation and impaired left ventricular (LV) systolic performance. There has been consistent evidence of intramyocardial lipid accumulation reflecting a compensatory shift in myocardial preference for fatty acids in the absence of insulin mediated glucose uptake.54,56

Alterations in SERCA2 have been reported in association with the hyperglycemia in STZ induced diabetes leading to decreased SR calcium sequestration and intracellular calcium overload.54,55 Decreases in contractile proteins such as α-actin and myosin ATPase activity have also been noted in association with shifts in myosin heavy chain isoforms from α to β, contributing to decreased systolic tension development.

The functional consequences of these cellular effects have been studied in cardiomyocytes, isolated perfused hearts and in vivo in rats with STZ induced diabetes. Abnormalities in diastolic function (increased LV end-diastolic pressure and operating chamber stiffness) can be observed in isolated heart preparations within 7 days, with significant decreases in LV systolic pressure, LV developed pressure, and LV dP/dt max evident within 3 weeks and progressing to profound systolic dysfunction over 1 year.60–62 Notably, these impairments in diastolic and systolic dysfunction occur in the absence of significant changes in myocardial perfusion.56,60 These important observations indicate that diastolic abnormalities, both impaired relaxation and increased stiffness, occur in the absence of hypertrophy and precede by weeks the onset of systolic dysfunction.60 Equally important is the observation that administration of insulin in type 1 diabetic rats partially corrects the systolic abnormalities in association with restoration of contractile proteins, even though modest hyperglycemia persists.54

These studies suggest that experimental type 1 diabetes, characterized principally by hyperglycemia is associated with altered calcium handling, impaired diastolic function, altered contractile proteins, and progressive systolic dysfunction as the magnitude and duration of the hyperglycemia progresses.54,55,58,59 These abnormalities occur in the absence of myocyte hypertrophy or fibrosis. The findings are consistent with a dominant influence of hyperglycemia and the absence of the influence of insulin. Thus, hyperglycemia alone is sufficient to account for the functional, but not necessarily the structural, changes observed in diabetic cardiomyopathy.

Models of Hyperinsulinemia With or Without Hyperglycemia

Models of type 2 diabetes are metabolically distinct from type 1 diabetes largely related to increased plasma insulin levels associated with altered cellular insulin action. Increased NEFAs and marked hyperinsulinemia are early accompaniments, whereas hyperglycemia is a later development attributable to exhaustion of pancreatic β-cell reserves. However, the cardiac manifestations in experimental models of type 2 diabetes vary considerably based on the onset and severity of these metabolic perturbations, as well as the complex interactions of intramyocardial lipids, insulin, and glucose on the cardiomyocyte structure and function.

Many of the commonly used experimental models of type 2 diabetes are associated with obesity caused by genetic perturbations in the Ob gene and its product, leptin.63–67 Leptin is a 16-kDa peptide produced by adipocytes that acts via specific receptors on the hypothalamus to inhibit food intake and increase energy expenditure. Notably, leptin receptors have been identified in the rat myocardium and regulate fatty acid oxidation independent of effects on the acetyl CoA-malonyl CoA axis.65 Leptin has also been shown to stimulate myocyte hyperplasia in rats and humans through both PI3-K– and ERK1/2-dependent mechanisms, similar to insulin. The metabolic phenotype associated with both leptin-deficient (ob/ob) and the leptin receptor–deficient (db/db) mice include obesity, insulin resistance, compensatory hyperinsulinemia, hypertriglyceridemia, and various degrees of hyperglycemia.

The cardiac phenotype of the ob/ob (leptin-deficient) mice has been studied both early and later in its development with varying results. There is evidence of LV hypertrophy and intramyocardial lipid accumulation both early and late, suggesting that hyperleptinemia is not necessary for the
development of LV hypertrophy. At 3 months with normal fasting glucose but impaired glucose tolerance, LV systolic, diastolic, and developed pressures are normal, but there is evidence of decreased cardiac power in isolated, working heart preparations. Notably, the degree of functional impairment varies depending on the concentrations of palmitate and insulin in the perfusate. In contrast, LV systolic function is preserved at both 3 months and 6 months when intact ob/ob mice are studied in vivo by echocardiography, whereas impaired diastolic function has been noted in some studies.

The hyperleptinemic db/db (leptin receptor–deficient) mice have a similar metabolic phenotype, but more profound hyperglycemia (30 to 50 mmol/L) manifest earlier in development. The hyperglycemic db/db mice have no cardiac hypertrophy at 3 months, despite combined hyperinsulinemia and hyperleptinemia, but develop LV hypertrophy later. In isolated working hearts, db/db mice have normal LV systolic and developed pressures but increased ventricular stiffness and impaired cardiac power. However, systolic function is preserved in db/db mice at 6 months when studied in vivo. The conflicting data as to the nature and extent of cardiac functional abnormalities between working heart and intact preparations can be reconciled by considering differences in substrate availability between the preparations. Hormone and substrate concentrations are limited in the isolated, crystalloid perfused hearts, whereas alternative substrates (lactate and pyruvate) and metabolic hormones are available in physiological concentrations in the intact models. Under circumstances in which a full array of substrates is available, LV systolic function is preserved. Notably, both models are associated with the development of cardiac hypertrophy independent of plasma leptin levels or action, suggesting that hyperleptinemia is not necessary for the development of cardiac hypertrophy in type 2 diabetes.

Finally, in contrast to the cardiac phenotype in models of type 1 diabetes, systolic performance is largely preserved even in the presence of profound hyperglycemia, provided that insulin is present. Instead, myocardial hypertrophy is the most commonly observed abnormality with increased chamber stiffness seen in some cases.

A similar evolution in cardiac phenotype is evident in genetically engineered rat models involving the absence of a functional leptin receptor. The Zucker fatty (ZF) rat is characterized metabolically by hyperleptinemia and consequent obesity, hyperlipidemia, and marked hyperinsulinemia with the late onset of hyperglycemia. As such, the model is characteristic of obesity and insulin resistance early (3 to 6 months). In contrast, the Zucker diabetic fatty (ZDF) rat has a similar genetic background but demonstrates earlier hyperglycemia, consistent with metabolic features of type 2 diabetes.

The morphological features of the ZF rat include increased intramyocardial lipid and increased myocardial mass. Hypertrophy is evident in individual myocytes and whole hearts where there is an associated expansion in the extracellular matrix. However, cardiac functional abnormalities have been observed inconsistently in isolated heart preparations with decreased cardiac power and systolic wall stress in some studies, whereas LV pressures and LV dP/dt and the rate-pressure product are maintained in others. Diastolic abnormalities have been noted early with prolonged isovolumic relaxation, whereas chamber stiffness was reported to be normal at 12 months.

In contrast to the ZF rats, the ZDF rats do not demonstrate consistent increases in cardiac mass. At 2 months, there is increased mass in the presence of marked hyperinsulinemia at a time when glucose levels are normal. However, by 3 months, there is no increase in mass when plasma glucose levels are high (27 mmol/L) and plasma insulin levels are reduced. Frederdsorf et al established the importance of the balance between hyperglycemia and hyperinsulinemia in 5-month-old ZDF rats by controlling hyperglycemia with exogenous insulin and demonstrating increased cardiac mass, whereas ZDF rats that remained persistent hyperglycemic had no increase in mass. In isolated heart preparations, the magnitude of systolic dysfunction in ZDF rats tends to be greater when accompanied by severe hyperglycemia. These effects are dependent on the substrate availability in the perfusate. In contrast, studies in intact ZDF reveal intact systolic function and myocardial hypertrophy, impaired flow reserve, and diastolic relaxation.

Thus, hyperinsulinemic ZF rats have myocardial hypertrophy and variable degrees of diastolic abnormalities, whereas the diabetic ZDF rats have smaller increases in cardiac mass and impairments in LV systolic function in isolated hearts but not intact models. These findings are consistent with the cellular effects of hyperinsulinemia to induce cardiac hypertrophy in contrast to the effects of hyperglycemia that mitigate hypertrophy and affect systolic dysfunction to a greater extent. Whether the observed abnormalities in diastolic function are a consequence of hypertrophy or hyperglycemia remains unresolved.

Models of Increased Intramyocardial Lipid Without Hyperinsulinemia or Hyperglycemia

The model of cardiac specific overexpression of PPARα in mice is associated with cardiac contractile dysfunction that is mediated by increased NEFA uptake and intracellular accumulation. Although the cardiac phenotype is dramatic both at baseline and in response to a superimposed cardiac insult, the model does not possess characteristic features of diabetes. However, this model is particularly useful in studying the contribution of excess intracellular lipid accumulation to cardiac contractile dysfunction, in the absence of hyperglycemia and hyperinsulinemia. Recent data using transgenic murine models of cardiac specific overexpression of fatty acid transport protein (FATP) demonstrated a cardiac phenotype that features diastolic dysfunction. Taken together, it is abundantly clear that increased circulating NEFAs, a ubiquitous feature of both type 1 and 2 diabetes, contribute fundamentally not only to the development of both insulin resistance and compensatory hyperinsulinemia but also can directly affect cardiac function.

Cardiovascular Manifestations in Humans With Type 1 and Type 2 Diabetes

The most commonly observed cardiac abnormalities in clinical studies of asymptomatic diabetics included LV hypertro-
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Unifying Hypothesis

There is an extensive body of epidemiological, clinical, and experimental evidence that supports the existence of a distinct form of cardiomyopathy related to pathogenic cellular and molecular changes that accompany diabetes mellitus. Figure 4 provides a unifying hypothesis as to the relationship between the common metabolic perturbations in diabetes and altered cardiac phenotypes. Specifically, the magnitude of ventricular hypertrophy may depend on the magnitude and duration of hyperinsulinemia that, in turn, may depend on magnitude and distribution of increasing NEFAs. In contrast, the extent of systolic dysfunction may depend more on the magnitude and duration of hyperglycemia and the presence or absence of insulin. Diastolic abnormalities may occur as a consequence of either hypertrophy or hyperglycemia. As such, hypertrophy and diastolic abnormalities are observed most commonly and earlier than systolic abnormalities and thus dominate the clinical findings. The paradigm reconciles the distinctive cardiovascular features attributable to type 1 (hyperinsulinemic/hyperglycemia→systolic dysfunction) and type 2 (hyperinsulinemic/hyperglycemic→hypertrophy and diastolic dysfunction) diabetes in experimental models studied in vivo. In humans with type 1 diabetes, systolic dysfunction is less evident than in STZ-induced models because these patients receive exogenous insulin, making them metabolically akin to a type 2 diabetic from this mechanistic perspective. These findings are generally consistent with the established cellular consequences of increased NEFAs, hyperinsulinemia, and hyperglycemia on cardiac structure and function. These insights afford the opportunity to design therapeutic approaches targeted at specific pathogenic mechanisms including suppression of lipolysis, maturation of adipocytes, and restoration of cellular insulin action, in addition to the traditional target of maintaining euglycemia.

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