Abstract—Diabetes mellitus increases the risk of heart failure independently of underlying coronary artery disease, and many believe that diabetes leads to cardiomyopathy. The underlying pathogenesis is partially understood. Several factors may contribute to the development of cardiac dysfunction in the absence of coronary artery disease in diabetes mellitus. This review discusses the latest findings in diabetic humans and in animal models and reviews emerging new mechanisms that may be involved in the development and progression of cardiac dysfunction in diabetes. (Circulation. 2007;115:3213-3223.)

Key Words: diabetes mellitus ■ fatty acids ■ heart failure ■ metabolism ■ obesity

The prevalence of diabetes mellitus is growing rapidly. It is estimated that globally the number of adults affected with diabetes will increase from 135 million in 1995 to 300 million by 2025. Patients with diabetes mellitus are at increased risk for cardiovascular diseases. Thus, cardiovascular complications are the leading cause of diabetes-related morbidity and mortality. Diabetes mellitus is responsible for diverse cardiovascular complications such as increased atherosclerosis in large arteries (carotids, aorta, and femoral arteries) and increased coronary atherosclerosis, which increases the risk for myocardial infarction, stroke, and limb loss. Microangiopathy contributes to retinopathy and renal failure and may contribute to cardiac pathology as well. Diabetes mellitus also can affect cardiac structure and function in the absence of changes in blood pressure and coronary artery disease, a condition called diabetic cardiomyopathy. This term was introduced 30 years ago by Rubler et al, who described 4 diabetic patients with congestive heart failure and normal coronary arteries. Since then, diabetic cardiomyopathy has been defined as ventricular dysfunction that occurs independently of coronary artery disease and hypertension. In addition, diabetic cardiomyopathy may be characterized by diastolic dysfunction, which becomes more apparent in the presence of hypertension or myocardial ischemia (discussed in detail in the next section).

Human Studies

Many epidemiological and clinical studies have suggested the existence of a diabetic cardiomyopathy in humans. Diabetes mellitus is a well-recognized risk factor for developing heart failure. Indeed, the Framingham Heart Study showed that the frequency of heart failure is twice in diabetic men and five times in diabetic women compared with age-matched control subjects. This increased incidence of heart failure in diabetic patients persisted despite correction for age, hypertension, obesity, hypercholesterolemia, and coronary artery disease. Studies using independent population databases have provided similar results, revealing increased heart failure rates in subjects with diabetes mellitus in cross-sectional analyses and increased risk for developing heart failure in prospective analyses, even after correction for confounding variables. Echocardiographic changes consistent with systolic dysfunction and left ventricular (LV) hypertrophy have been described in a number of studies of diabetic populations and may portend an increased risk for the subsequent development of heart failure, particularly in the presence of coexisting hypertension. Diabetic cardiomyopathy in humans also is characterized by diastolic dysfunction, which may precede the development of systolic dysfunction. Indeed, echocardiography performed in 87 patients with type 1 diabetes mellitus without known coronary artery disease revealed diastolic dysfunction with a reduction in early diastolic filling, an increase in atrial filling, an extension of isovolumetric relaxation, and increased numbers of supraventricular premature beats. In similar subjects with uncomplicated type 1 diabetes without clinically apparent macrovascular or microvascular complications, Carugo et al reported early structural and functional cardiac alterations such as increased LV wall thickness and LV mass index, an age-related decline in ejection fraction, and an age-related increase in diastolic diameter. Similar approaches in well-controlled subjects with type 2 diabetes have revealed a prevalence of diastolic dysfunction of up to 30%. The use of flow and tissue Doppler techniques suggests even higher prevalence of diastolic dysfunction (as high as 40% to 60%) in community surveys and in smaller studies of individuals with type 2 diabetes.
In Vivo and Ex Vivo Data for Cardiac Dysfunction in Animal Models of Type 1 and Type 2 Diabetes Mellitus

| Animal Studies |

In animal models of diabetes, several functional and structural alterations of the heart or in cardiac muscle have been documented. The Table summarizes representative findings on cardiac function using in vivo and ex vivo measurement techniques in a variety of type 1 and type 2 diabetic rodent models. In interpreting these results, we must consider differences in the animal models examined. Thus, in most studies of type 1 diabetes mellitus, diabetes is induced after administration of the pancreatic beta-cell toxin streptozotocin, and most studies of type 2 diabetes mellitus have been performed in genetic models of obesity and insulin resistance such as the Zucker fatty rat or db/db mice, both of which have mutations that impair leptin receptor signaling, or ob/ob mice, which lack leptin. Moreover, because diabetes mellitus develops at varying tempos in these models, it is important to bear in mind that studies performed in animals before the onset of diabetes may reflect changes that are secondary to the underlying obesity and insulin resistance, and studies performed after the onset of diabetes may reflect the added effects of hyperglycemia of various durations. Most studies have been performed in isolated perfused hearts and reveal depressed cardiac function (recently reviewed by Severson and more recently supported by other studies).

Fewer studies have reported normal function in vivo. In vivo studies in these rodent models have provided evidence for systolic and diastolic dysfunction by echocardiography, but in some studies using invasive LV catheterization in mouse models of obesity and diabetes mellitus, LV contractility as determined by dP/dt was initially increased and may reflect the impact of the increased plasma volume and perhaps sympathetic activation associated in part with the underlying obesity. These initial observations were further clarified by Van den Bergh et al., who assessed hemodynamic changes in db/db mouse hearts in vivo using a pressure-volume catheter. They observed decreased contractility using load-independent variables such as preload recruitable stroke work, but steady-state measurements of cardiac output and other load-dependent parameters were elevated in db/db mice compared with control mice because of favorable loading conditions, specifically increased preload and decreased afterload.

The impact of diabetes mellitus on ischemia/reperfusion injury in rodent models has been examined both in vitro and in vivo. Although some controversy exists on whether diabetic hearts are more susceptible to injury when analyzed ex vivo, most in vivo studies have supported a greater degree of reduction in LV function and accelerated LV remodeling in the hearts of diabetic animals after coronary artery ligation. Thus, it is likely that the diabetic milieu and associated changes in the myocardium sensitize the diabetic heart to dysfunction after ischemic injury. Studies in models of type 2 diabetes mellitus and insulin resistance suggest that insulin resistance per se might contribute to reduced myocardial recovery after ischemia. For example, genetic models of obesity and insulin resistance such as Zucker rats and db/db mice and mice with diet-induced obesity and insulin resistance exhibit impaired recovery of cardiac function after in vivo coronary artery ligation. Changes may be independent of infarct size, which is unchanged in models fed high-fat diets but increased in db/db mice. Moreover, treatment of Zucker rats with insulin sensitizing agents such as thiazolidinedione improves postischemic recovery in vitro and in vivo. Uncoupling protein-diaphorase toxin A transgenic mice, which are a model of insulin resistance and obesity without diabetes, also exhibit impaired functional recovery in vitro after ischemia. In contrast, postischemic recovery of isolated perfused hearts is normal in db/db mice at a time when they are obese and insulin resistant but before the onset of diabetes, whereas ischemic recovery is impaired after the onset of diabetes. Taken together, these data suggest that insulin resistance per se may increase the susceptibility of the rodent heart to ischemia/reperfusion injury and that the coexistence of hyperglycemia might exacerbate the phenotype.

Important caveats exist when extrapolating findings obtained in animal models of diabetes to humans. For example, cardiac physiology such as heart rate is different in rodents and humans, and rodent models are less likely to develop atherosclerotic disease in coronary arteries and spontaneous ischemia, which exists in many humans with diabetes mellitus. Important differences also exist in the hormonal milieu and the concentrations of lipids. Finally, most animal studies...
are performed in animals with uncontrolled or poorly controlled diabetes, whereas most human subjects will be on some form of therapeutic intervention. Nevertheless, animal models provide the opportunity to conduct mechanistic studies, which in some cases have been confirmed in human studies.

**Pathogenesis of Diabetic Cardiomyopathy: Mechanisms**

The pathogenesis of diabetic cardiomyopathy is multifactorial. Several hypotheses have been proposed, including autonomic dysfunction, metabolic derangements, abnormalities in ion homeostasis, alteration in structural proteins, and interstitial fibrosis. Sustained hyperglycemia also may increase glycation of interstitial proteins such as collagen, which results in myocardial stiffness and impaired contractility. In this review, we focus on mechanisms that are involved in decreasing myocardial contractility in diabetes mellitus. These are (1) impaired calcium homeostasis, (2) upregulation of the renin-angiotensin system, (3) increased oxidative stress, (4) altered substrate metabolism, and (5) mitochondrial dysfunction.

**Impaired Calcium Homeostasis**

Intracellular calcium (Ca²⁺) is a major regulator of cardiac contractility. In the cardiomyocyte, Ca²⁺ influx induced by activation of voltage-dependent L-type Ca²⁺ channels on membrane depolarization triggers the release of Ca²⁺ via Ca²⁺ release channels (ryanodine receptors) of sarcoplasmic reticulum (SR) through a Ca²⁺-induced Ca²⁺ release mechanism. Ca²⁺ then diffuses through the cytosolic space to reach contractile proteins, binding to troponin C and resulting in the release of the inhibition induced by troponin I. By binding to troponin C, the Ca²⁺ triggers the sliding of thin and thick filaments, which results in cardiac force development and/or contraction. [Ca²⁺]i then returns to diastolic levels mainly by activation of the SR Ca²⁺ pump (SERCA2a), the sarcolemmal Na⁻-Ca²⁺ exchanger, and the sarcolemmal Ca²⁺ ATPase. It has long been appreciated that calcium and other ion homeostasis is altered in diabetic cardiomyocytes (recently reviewed by Cessario et al). The mechanisms by which disturbed calcium homeostasis alters cardiac function in diabetes include reduced activity of ATPases, decreased ability of the SR to take up calcium, and reduced activities of other exchangers such as Na⁺-Ca²⁺ and the sarcolemmal Ca²⁺ ATPase. Indeed, the SR Ca²⁺ store and rates of Ca²⁺ release and reuptake into SR were depressed in type 1 diabetic rat myocytes. The rate of Ca²⁺ efflux via sarcolemmal Na⁺-Ca²⁺ exchanger also was depressed. However, no change occurred in the voltage-dependent L-type Ca²⁺ channel current that triggers Ca²⁺ release from the SR. The depression in SR function was associated with decreased SR Ca²⁺ ATPase and ryanodine receptor proteins and increased total and nonphosphorylated phospholamban proteins. In the db/db mouse model of type 2 diabetes mellitus, Ca²⁺ efflux in the cardiomyocyte was reduced, SR Ca²⁺ load was depressed, ryanodine receptor expression was reduced, and Ca²⁺ influx through the Na⁺-Ca²⁺ exchanger was increased. Furthermore, decreased cardiac expression of SERCA2a or the Na⁺-Ca²⁺ exchanger has been observed in type 1 and type 2 diabetes. Trost et al observed that transgenic mice overexpressing SERCA2a were protected from streptozotocin-induced cardiac dysfunction, suggesting that altered calcium handling contributes to impaired cardiac function in diabetes mellitus. Technical challenges are involved in performing similar studies in humans. Studies in humans with heart failure have focused on examining changes in expression levels of proteins or genes involved in calcium signaling or measuring calcium concentrations and SR Ca²⁺ uptake in cardiomyocytes isolated from failing hearts of transplant recipients at the time of surgery. Such analyses remain to be conducted in patients with diabetic cardiomyopathy. However, a recent study described depressed myofilament function as a result of decreased Ca²⁺ sensitivity in skinned fibers obtained from diabetic patients at the time of coronary artery bypass surgery. This limited clinical study supports previous studies in animals. However, more studies are required to characterize the mechanisms responsible for altered calcium handling in patients with diabetic cardiomyopathy.

**Activation of the Renin-Angiotensin System**

The role of activation of the renin-angiotensin system in the development of diabetic cardiomyopathy is well recognized. Angiotensin II receptor density and mRNA expression are elevated in the diabetic heart. Activation of the renin-angiotensin system during diabetes mellitus has been shown to be associated with increased oxidative damage and cardiomyocyte and endothelial cell apoptosis and necrosis in diabetic hearts, which contributes to the increased interstitial fibrosis. Blockade of the renin-angiotensin system in streptozotocin-treated rats attenuated cardiac dysfunction partially through restoration of sarcoplasmic calcium handling. In a parallel study, blockade of the renin-angiotensin system reversed diabetes-induced Ca²⁺ loading of the SR and depletion of ryanodine receptors. Inhibition of the renin-angiotensin system was shown to reduce reactive oxygen species (ROS) production in streptozotocin-induced diabetic rats, similar to the effect observed with antioxidant treatment. Moreover, treatment of spontaneously diabetic (BB) rats with the angiotensin-converting enzyme inhibitor captopril has a cardioprotective effect.

**Increased Oxidative Stress**

Increased ROS production in the diabetic heart is a contributing factor in the development and the progression of diabetic cardiomyopathy (the Figure). Cumulative superoxide-mediated damage or cellular dysfunction results when an imbalance exists in ROS generation and ROS-degrading pathways. Increased ROS generation and impaired antioxidant defenses could both contribute to oxidative stress in diabetic hearts. Several groups have shown that ROS is overproduced in both type 1 and type 2 diabetes. Under physiological states, most of the ROS generated within cells arises from mitochondria. Whereas increased mitochondrial ROS generation has been shown in various tissues such as endothelial cells that are exposed to hyperglycemia, relatively few studies to date have directly measured mito-
Increased free FA (FFA) activates PPAR-α signaling, leading to the increased transcription of many genes involved in FA oxidation. Increased FA oxidation leads to the generation of ROS at the level of the electron transport chain. ROS, which also can be generated by extramitochondrial mechanisms such as NADPH oxidase, plays a critical role in several pathways involved in the pathogenesis of diabetic cardiomyopathy, including lipotoxicity, cell death, and tissue damage, as well as mitochondrial uncoupling and reduced cardiac efficiency. TG indicates triglycerides; GLUTs, glucose transporters; PDK4, pyruvate dehydrogenase kinase 4; MCD, malonyl-coenzyme A decarboxylase; MCOA, malonyl-coenzyme A; ACOA, acetyl-coenzyme A; ACC, acetyl coenzyme A carboxylase; CPT1, carnitine palmitoyl-transferase 1; PDH, pyruvate dehydrogenase; CE, cardiac efficiency; PKG, protein kinase C; and AGE, glycation end products.

**Potential contributors to the development of diabetic cardiomyopathy.**

In diabetes mellitus, increased ROS also might contribute to mitochondrial uncoupling, which could impair myocardial energetics in diabetes. This aspect will be discussed in more detail later in this review. Strategies that enhance mitochondrial ROS scavenging systems have been shown to be efficacious in reducing diabetes-induced cardiac dysfunction. Overexpression of metallothionein, catalase, and manganese superoxide dismutase in the heart reversed diabetic cardiomyopathy in animal models of both type 1 and type 2 diabetes. Thus, strategies that either reduce ROS or augment myocardial antioxidant defense mechanisms might have therapeutic efficacy in improving myocardial function in diabetes mellitus.

**Altered Substrate Metabolism: Metabolic Cardiomyopathy**

Altered myocardial substrate and energy metabolism has emerged as an important contributor to the development of diabetic cardiomyopathy. Diabetes mellitus is characterized by reduced glucose and lactate metabolism and enhanced fatty acid (FA) metabolism. Despite an increase in FA use in diabetic hearts, it is likely that FA uptake exceeds oxidation rates in the heart, thereby resulting in lipid accumulation in the myocardium that may promote lipotoxicity. Lipid intermediates such as ceramide might promote apoptosis of cardiomyocytes, thus representing another mechanism that might lead to cardiac dysfunction.

Multiple mechanisms contribute to the substrate switching that characterizes the diabetic heart. These include increased delivery of FAs, decreased insulin signaling, and activation of transcriptional pathways such as the peroxisome proliferator-activated receptor-α (PPAR-α)/PGC-1 signaling network that regulates myocardial substrate use. Thus, activation of PPAR-α increases the expression of pyruvate dehydrogenase kinase 4, which reduces glucose oxidation. Concomitantly, PPAR-α activation increases the expression levels of genes...
such as CD36, which regulates cellular FA uptake, and malonyl CoA decarboxylase, which degrades malonyl CoA, thereby derepressing carnitine palmitoyl transferase-1 and stimulating mitochondrial FA uptake. In addition, genes involved in β-oxidation such as medium- and long-chain acyl CoA dehydrogenase and hydroxy acyl CoA dehydrogenase also are transcriptional targets of PPAR-α (the Figure).

In young ob/ob and db/db mice, increased FA oxidation and decreased glucose oxidation rates were not associated with increased expression of PPAR-α, PGC-1, or its transcriptional targets. Myocardial glucose use is reduced as early as 10 days on a high-fat diet and is accompanied by reduced insulin signaling. Thus, early in the course of obesity, it is likely that changes in myocardial substrate use reflect changes in substrate availability such as increased myocardial delivery of FAs and triglycerides. The reciprocal reduction in glucose use probably reflects allosteric inhibition of glucose use in the face of an increase in FA use (Randle phenomenon). It also is possible that impaired insulin signaling may have independent effects to reduce myocardial glucose use, as was observed in the hearts of mice with cardiomyocyte-restricted deletion of insulin receptors. As caloric excess and/or obesity become more longstanding, activation of transcriptional pathways such as PPAR-α/PGC-1-mediated signaling increases the expression genes involved in FA oxidation and FA import such as carnitine palmitoyl transferase-1 and medium- and long-chain acyl CoA dehydrogenase and FA transporters such as FATP1 and CD36, which contributes further to the metabolic changes in these hearts (the Figure). A second mechanism that may contribute to increased myocardial FA uptake in type 2 diabetic rodents is redistribution of CD36 to the plasma membrane.

It is important to emphasize that in many in vitro studies, isolated perfused hearts are exposed to a simple mixture of 2 substrates, namely glucose and FAs. Studies using multiple substrates such as ketones and lactate in addition to glucose and FA indicate that isolated hearts from diabetic animals use less lactate as well and glucose and that the degree of FA use might be higher at low FA concentrations but not necessarily at high FA concentrations. A recent in vivo analysis using tracer techniques designed to determine in vivo metabolism of glucose and FA suggested that FA use might not necessarily be increased in vivo because of increased use of other substrates such as ketones and that increased FA use was driven by increased concentrations of FA in db/db mice. In fact, increased overall FA use was observed only under pseudofed conditions (glucose infusion) but not under fasting conditions. Importantly, these diabetic hearts demonstrated significant impairment in metabolic flexibility in terms of their ability to alter their substrate use when concentrations of metabolic substrates used by the heart were manipulated. This in vivo study confirms the existence of altered myocardial substrate use in diabetic hearts but raises important caveats that should be considered when the results obtained in isolated hearts are interpreted.

An important question is whether the changes in patterns of substrate use that characterize diabetic hearts directly contribute to impaired cardiac function. Studies of short-term diabetes mellitus revealed that changes in substrate fluxes occurred coincidentally with impaired myocardial function. Moreover, in longstanding type 1 diabetes mellitus, insulin replacement increased glucose use, reversed many of the metabolic abnormalities associated with diabetes, and reversed myocardial dysfunction. In models of type 2 diabetes mellitus, results of therapeutic interventions on cardiac function and metabolism have been variable and dependent on the model. Treatment of Zucker diabetic rats with PPAR-γ agonists restored cardiac function and reversed lipotoxicity. In addition, an increase occurred in glucose metabolism that accompanied increasing cardiac function. This therapeutic approach had 2 major metabolic consequences. First, a nearly complete reversal of lipotoxicity took place. Second, glucose use increased. It is not possible from these studies to determine the relative contribution of increased glucose use versus a reduction in lipotoxicity to the increase in cardiac function. Studies in lipotoxic transgenic mouse models have shown that reversal of myocardial steatosis by overexpression of a human apolipoprotein B transgene or by an increase in leptin concentrations normalizes cardiac function. It should be noted that in contrast to other rodent models of type 2 diabetes mellitus, Zucker rats may have a limitation in FA oxidation particularly under conditions of increased FA supply. In transgenic mice that are null for the PPAR-α gene that also have reduced FA oxidative capacity, the reduction in contractile reserve can be reversed by increasing the delivery of glucose by transgenic overexpression of the GLUT1 glucose transporter. Thus, it is likely that switching to glucose and reducing lipotoxicity may both contribute independently to the beneficial effect of PPAR-γ agonist treatment in this model. In contrast, db/db mice have increased rates of FA oxidation, which increase further as FA supply is increased. Treatment of db/db mice at different ages with PPAR-α or PPAR-γ agonists failed to reverse cardiac dysfunction despite a reduction in FA oxidation and increased glucose use that occurred concomitantly with the normalization of systemic metabolic homeostasis. The lack of an immediate benefit of normalizing substrate metabolism in db/db mice might reflect the severity of diabetes in this model or the persistence of mitochondrial dysfunction that is not normalized by short-term correction of metabolic abnormalities and myocardial substrate flux rates. If this hypothesis is correct, then one would expect high-energy phosphate metabolism to remain depressed after short-term PPARγ or PPARα ligand treatment of db/db mice. Prevention of altered substrate metabolism in these mice by perinatal overexpression of the GLUT4 glucose transporter prevented cardiac dysfunction in db/db mice, suggesting that metabolic modulation to sustain glucose use might prevent cardiac dysfunction in this model of severe type 2 diabetes mellitus. However, to be effective in this model of severe diabetes, the metabolic modulation either has to occur early in the course of diabetes or has to be of long duration.

An important recent contribution to our understanding of the metabolic disturbances associated with diabetes mellitus is the observation that increased myocardial FA use in diabetic mouse models is associated with increased myocardial oxygen consumption. Thus, cardiac efficiency, which is
the ratio of energy output (cardiac work) to energy input (MV\textsubscript{O}2) is reduced in diabetic hearts.\textsuperscript{33,35,48,148} Whether reduced cardiac efficiency contributes to the development of diabetic cardiomyopathy is still unknown. However, reduced cardiac efficiency may render the heart more vulnerable to hemodynamic stress such as that which occurs during ischemia/reperfusion, when the coupling between oxygen consumption and ATP production is very important. It was recently demonstrated, for example, that the impairment in functional recovery of db/db mice after ischemia/reperfusion could be ameliorated by very high concentrations of insulin and glucose in perfusates, which increased glucose use and enhanced cardiac efficiency.\textsuperscript{149} A number of potential mechanisms exist for reduced cardiac efficiency in diabetic hearts. Some studies suggest that most of the oxygen wasting occurs for noncontractile processes.\textsuperscript{148} Increased expression of mitochondrial and cytosolic thioesterases also has been proposed to contribute to reduced cardiac efficiency by increasing futile cycling of FAs.\textsuperscript{150,151} We and others have focused on the possibility that mitochondrial uncoupling results in a reduction in cardiac efficiency in diabetes mellitus on the basis of an increase in uncoupling protein expression and/or activation.\textsuperscript{33,152,153}

Recent studies in humans have supported many of the mechanisms that have been elucidated in animal studies. Thus, positron emission tomography studies of subjects with type 1 diabetes mellitus revealed increased myocardial FA use and reduced glucose oxidation,\textsuperscript{154} supporting earlier studies that used invasive coronary sinus and arterial sampling to determine myocardial substrate balance.\textsuperscript{155} Altered metabolism in these type 1 diabetic patients was associated with increased myocardial oxygen consumption (MV\textsubscript{O}2) and increased concentrations of serum free FA. Using similar techniques, Peterson et al\textsuperscript{156} demonstrated increased FA oxidation and MV\textsubscript{O}2 and reduced cardiac efficiency in obese insulin-resistant women. Cardiac efficiency was inversely associated with insulin resistance, glucose intolerance, and obesity. It is likely that these changes may contribute to the pathogenesis of decreased cardiac performance in obesity and insulin-resistant states. Treatment of type 2 diabetes mellitus with the PPAR-\gamma agonist rosiglitazone increased myocardial glucose uptake in patients with underlying coronary disease,\textsuperscript{157} and in another cohort of diabetic subjects, myocardial glucose uptake was positively correlated with LV function.\textsuperscript{158} Thus, it will be important in future studies to determine whether therapies that will correct abnormal myocardial substrate metabolism in diabetes mellitus will translate to lower prevalence of heart failure or improved long-term survival. We may need to await the generation of new classes of therapeutic agents, given concerns that PPAR-\gamma agonist therapy might increase the risk of heart failure that occurs on the basis of plasma volume expansion.\textsuperscript{159}

Mitochondrial Dysfunction

Recent studies of mitochondria have reignited interest in a role for mitochondrial dysfunction in the pathogenesis of diabetic cardiomyopathy.\textsuperscript{153,160,161} Diabetes mellitus causes functional and structural alterations in mitochondria. Impaired mitochondrial function was initially reported almost 25 years ago when Kuo et al\textsuperscript{162} showed depressed state 3 respiration in db/db heart mitochondria. This study was followed by others showing reduced mitochondrial oxidative capacity in type 1 diabetes.\textsuperscript{163–166} We have recently demonstrated decreased mitochondrial respiration and reduced protein expression of the oxidative phosphorylation components in obese type 2 diabetic mice.\textsuperscript{33} These alterations contribute to cardiac dysfunction because they reduce ATP production, which we speculate will diminish myocardial high-energy phosphate reserves, thereby contributing to impaired myocardial contractility. In addition to reduced oxidative phosphorylation capacity, mitochondria from hearts of type 1 diabetic animals exhibit a lower creatine phosphate activity,\textsuperscript{167,168} lower ATP synthase activity,\textsuperscript{163} and lower creatine-stimulated respiration.\textsuperscript{169} Additional mitochondrial defects in diabetes also may play a role in the development of cardiac dysfunction. These defects include decreased mitochondrial calcium uptake\textsuperscript{164} attributed in part to enhanced permeability transition.\textsuperscript{170}

Mitochondrial dysfunction in diabetes may reflect in part transcriptional repression of genes involved in oxidative phosphorylation components but not genes involved in FA oxidation. Thus, a reduction in mRNA levels of cytochrome b and ATP synthase subunit 6 (mitochondria-encoded genes) was found in streptozotocin-induced diabetic hearts.\textsuperscript{171,172} This was associated with a reduction in the binding capacity of mitochondrial transcription factor A to mitochondrial DNA. In addition, proteomic analysis of the diabetic heart also revealed reduced expression of proteins of the electron transport chain, creatine kinase, and the voltage-dependent anion channel 1, whereas the expression of \(\beta\)-oxidation proteins was increased.\textsuperscript{119} These changes could lead to mitochondrial dysfunction in a number of ways. Increased \(\beta\)-oxidation will increase the delivery of reducing equivalents to the electron transport chain. However, a limitation in oxidative phosphorylation components might result in increased superoxide production, which in turn might uncouple mitochondria and reduce the efficiency of ATP generation, which compounds existing defects in respiratory capacity.\textsuperscript{33,153} Indeed, perfusion of ob/ob hearts with FAs clearly increased mitochondrial oxygen consumption in mitochondria from ob/ob mice that was associated with a further reduction in ATP generation, indicating mitochondrial uncoupling.\textsuperscript{33} We speculate that this occurs in part because of increased delivery of reducing equivalents from \(\beta\)-oxidation to an electron transport chain that is impaired. The net result is ROS-mediated mitochondrial uncoupling. It also is possible that mitochondrial uncoupling could represent an adaptive mechanism in diabetic hearts to reduce membrane potential and ROS. Future studies in which expression levels or the activity of proteins that mediate mitochondrial uncoupling is manipulated are required to clarify whether mitochondrial uncoupling is adaptive or maladaptive in diabetic hearts.

Mitochondrial protein nitration (as an index of oxidative damage) was increased in hearts from alloxan-induced diabetes.\textsuperscript{173} Mitochondrial hydrogen peroxide production was increased and glutathione levels were reduced in diabetic hearts, and these changes were attenuated by rotenone, thereby suggesting a mitochondrial source for ROS.\textsuperscript{171,174}
Oxidative stress may therefore alter mitochondrial proteins, leading to mitochondrial dysfunction. Overexpression of ROS-detoxifying proteins (metallothionein, catalase, and manganese superoxide dismutase) reverses mitochondrial dysfunction and cardiomyopathy induced by diabetes. These data suggest an important role for mitochondrial dysfunction in limiting myocardial high-energy phosphate metabolism in diabetes mellitus. Recent studies in humans have provided support for a role of mitochondrial dysfunction in diabetic cardiomyopathy. A reduction in the ratio of phosphocreatine to ATP has been observed in patients with type 1 and type 2 diabetes mellitus without clinically significant coronary artery disease and correlates with indexes of diastolic dysfunction and with levels of serum free FAs. It will be of great interest to see the results of studies that will evaluate the impact of various therapeutic strategies on myocardial energetics and long-term cardiovascular outcomes in patients with diabetes.

Ultrastructural analyses have revealed increased mitochondrial proliferation in models of type 1 and type 2 diabetes mellitus and even in mouse models of the metabolic syndrome. Whereas evidence exists that these mitochondrial changes might be driven in part by activation of the PGC1-α/PPARα gene regulatory pathways, it is important to note that the predicted consequence of increased PGC1-α signaling, although promoting mitochondrial biogenesis, might not be sufficient in the context of diabetes to increase oxidative phosphorylation component capacity. This is supported by studies in mice with transgenic overexpression of PGC1-α in which mitochondrial biogenesis can be dissociated from a proportionate increase in mitochondrial function. It also is likely that other signaling pathways may play an important role in promoting mitochondrial biogenesis in the heart, and these remain to be elucidated. Gene knockouts of critical mitochondrial proteins such as the adenine nucleotide translocase and mitochondrial transcription factor A lead to increased mitochondrial biogenesis and cardiac myopathies. Thus, additional studies to elucidate the nature of potential additional mechanisms that promote mitochondrial biogenesis in diabetes mellitus are warranted. The other important conclusion that can be drawn from the studies performed to date is that an increase in cardiac mitochondria in diabetes does not necessarily imply an increase in myocardial energetics.

Summary and Perspectives
Diabetes mellitus is a growing public health problem that needs to be tackled at multiple levels such as prevention and health maintenance and aggressive management of associated comorbidities such as obesity, hypertension, and dyslipidemia. Cardiovascular disease remains the leading cause of mortality and morbidity in individuals with diabetes. The belief is widely held that the increase in cardiovascular mortality is a consequence of accelerated atherosclerosis. However, compelling epidemiological and clinical data indicate that diabetes mellitus increases the risk for cardiac dysfunction and heart failure independently of other risk factors such as coronary disease and hypertension. It is clear that coexisting morbidities accelerate the likelihood of developing cardiac dysfunction in diabetes. Recent research in humans and animals has provided novel insights into underlying molecular and pathophysiological mechanisms that increase the vulnerability of the diabetic heart to failure. It is hoped that as the mechanisms responsible for diabetic cardiomyopathy continue to be elucidated, they will provide the impetus for generating novel therapies tailored to reduce the risk of heart failure in individuals with diabetes mellitus, who will contribute significantly to a growing burden of heart failure that might accompany the growing epidemic of diabetes.

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