Role of changes in cardiac metabolism in development of diabetic cardiomyopathy

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An, Ding, and Brian Rodrigues. Role of changes in cardiac metabolism in development of diabetic cardiomyopathy. *Am J Physiol Heart Circ Physiol* 291: H1489–H1506, 2006. First published June 2, 2006; doi:10.1152/ajpheart.00278.2006.—In patients with diabetes, an increased risk of symptomatic heart failure usually develops in the presence of hypertension or ischemic heart disease. However, a predisposition to heart failure might also reflect the effects of underlying abnormalities in diastolic function that can occur in asymptomatic patients with diabetes alone (termed diabetic cardiomyopathy). Evidence of cardiomyopathy has also been demonstrated in animal models of both Type 1 (streptozotocin-induced diabetes) and Type 2 diabetes (Zucker diabetic fatty rats and db/db or ob/ob mice). During insulin resistance or diabetes, the heart rapidly modifies its energy metabolism, resulting in augmented fatty acid and decreased glucose consumption. Accumulating evidence suggests that this alteration of cardiac metabolism plays an important role in the development of cardiomyopathy. Hence, a better understanding of this dysregulation in cardiac substrate utilization during insulin resistance and diabetes could provide information as to potential targets for the treatment of cardiomyopathy. This review is focused on evaluating the acute and chronic regulation and dysregulation of cardiac metabolism in normal and insulin-resistant/diabetic hearts and how these changes could contribute toward the development of cardiomyopathy.

HEART DISEASE is a leading cause of death in diabetic patients (226, 253), with coronary vessel disease and atherosclerosis being primary reasons for the increased incidence of cardiovascular dysfunction (151, 225, 253). However, a predisposition to heart failure might also reflect the effects of underlying abnormalities in diastolic function that can be detected in asymptomatic patients with diabetes alone (24, 61, 74). These observations suggest a specific impairment of heart muscle (termed diabetic cardiomyopathy). Rodent models of chronic diabetes demonstrate abnormalities in diastolic left ventricular function, with or without systolic left ventricular dysfunction (73, 205, 219). Because diastolic dysfunction is also seen in patients with both Type 1 and Type 2 diabetes, it can be proposed that the diabetic state can directly induce abnormalities in cardiac tissue independent of vascular defects. Several etiological factors have been put forward to explain the development of diabetic cardiomyopathy, including an increased stiffness of the left ventricular wall associated with accumulation of connective tissue and insoluble collagen (9, 204, 212) and abnormalities of various proteins that regulate ion flux, specifically intracellular calcium (90, 235). More recently, the view that diabetic cardiomyopathy could also occur as a consequence of metabolic alterations has been put forward (146, 147, 149).

Because uninterrupted contraction is a unique feature of the heart, cardiac muscle has a high demand for provision of energy. Under normal physiological conditions, hearts can utilize multiple substrates, including fatty acids (FA), carbohydrate, amino acids, and ketones (15). Among these substrates, carbohydrates and FA are the major sources from which the heart derives most of its energy. In a normal heart, 70% of ATP generation is through FA oxidation, whereas glucose and lactate account for ~30% of energy provided to the cardiac muscle (86, 173, 210). It should be noted that the heart can rapidly switch its substrate selection to accommodate different physiological and pathophysiological conditions involving altered extracellular hormones, substrate availability, and workload (energy demand) (11, 130, 204, 217, 227). Acutely or chronically, this regulation occurs through various mechanisms. Although substrate switching is essential to ensure continuous ATP generation to maintain heart function, it has also been associated with deleterious consequences (17, 267).

In Type 1 and Type 2 diabetes mellitus, glucose uptake, glycolysis, and pyruvate oxidation are impaired. Additionally, lack of insulin function augments lipolysis and release of FA from adipose tissue. Under these conditions, the heart rapidly adapts to using FA exclusively for ATP generation. Chronically, this maladaptation is believed to play a key role in the development of cardiomyopathy. Hence, it is essential to identify and understand the mechanisms that control substrate utilization in the diabetic heart. This review discusses the acute and chronic cellular changes that modify cardiac metabolism and elucidate their roles in the development of cardiomyopathy.
INVITED REVIEW

ABNORMAL REGULATION OF CARDIAC SUBSTRATE METABOLISM IN DIABETES

DIABETIC CARDIOMYOPATHY

The central basis for diabetic heart failure is coronary disease associated with atherosclerosis (151, 225, 253). Because diabetes is often accompanied by hypertension and/or ischemic heart disease, which often causes diastolic dysfunction, it is difficult to attribute heart failure in these patients to diabetes alone (23). On the other hand, Type 1 or Type 2 diabetic patients have also been diagnosed with reduced or low-normal diastolic function and left ventricular hypertrophy in the absence of coronary heart disease or hypertension, identified as cardiomyopathy (24, 81, 192, 195, 200, 231). These abnormalities in asymptomatic diabetic patients potentially might predispose them to symptomatic heart failure when they develop hypertension or ischemic heart disease, particularly after myocardial infarction.

In animal models of Type 1 diabetes, either streptozotocin (STZ)-induced rats or genetic nonobese diabetic mice, systolic and diastolic dysfunction have been demonstrated using in vivo or in vitro measurements (177, 185, 232, 239). For example, systolic and diastolic dysfunction have been detected by using echocardiography in STZ diabetic animals (123, 177). With the use of in vivo catheterization of these animals, elevated left ventricular end-diastolic pressure and reduced left ventricular systolic pressure with diminished increase or decrease pressure over time (±dP/dt) were observed (124). Reduced peak left ventricular pressure and ±dP/dt were confirmed in ex vivo perfused STZ hearts (239). Recently, evidence of cardiomyopathy has also been reported in animal models of insulin resistance and Type 2 diabetes (ZDF rats and ob/ob or db/db mice) (5, 21, 30, 266). In db/db mice, systolic and diastolic dysfunction were detected by echocardiography (218). With the use of ex vivo perfused hearts from db/db mice, augmented left ventricular end-diastolic pressure and reduced cardiac output and cardiac power have also been observed (21). Given that rodents are resistant to atherosclerosis, these models provided strong evidence for the occurrence of diabetic cardiomyopathy. However, in another study, no evidence of impairment in cardiac function was detected using in vivo Langendorff perfusions of hearts from insulin resistant and obese Zucker rats (224) and Type 2 diabetic Zucker fatty (ZDF) rats (250). It is likely that such inconsistencies arose due to the rodent models used and the methods employed for evaluating heart function in the different studies.

It should be acknowledged that the features of cardiomyopathy between human diabetic patients and rodent diabetic models might be different. The development of diabetic cardiomyopathy is influenced by the severity and duration of alterations in plasma parameters such as insulin, leptin, glucose, and lipids. Given the discrepancy in changes in these hormones and substrates between human diabetic patients and rodent models of Type 1 and Type 2 diabetes, the etiology and severity of diabetic cardiomyopathy may vary (196). For example, STZ-induced diabetes exhibit severe hypoinsulinemia, whereas ob/ob mice show leptin deficiency, which are rare in human diabetes. Additionally, it has been suggested that STZ can directly impair the cardiac contractile function of isolated ventricular myocytes (256). Finally, although db/db mice and Zucker and ZDF rats exhibit hyperinsulinemia, hyperleptinemia, and hyperglycemia, the severity of these alterations vary between animal models and patients with diabetes (196). Taken together, experimental data obtained using animals models of diabetes should be used with caution when extrapolating to the human condition.

Cardiomyopathy is a complicated disorder, and several factors have been associated with its development. These include increased stiffness of the left ventricular wall associated with accumulation of connective tissue and insoluble collagen (204, 212), depressed autonomic function (73), impaired endothelium function and sensitivity to various ligands (e.g., β-agonists) (23), and abnormalities of various proteins that regulate ion flux, specifically intracellular calcium (90, 235). More recently, there is a generalized view that diabetic cardiomyopathy also occurs as a consequence of altered fuel metabolism. During insulin resistance or diabetes, glucose utilization is compromised. This alteration, together with increased FA supply, switches cardiac energy generation to utilization of FA. High FA uptake and metabolism not only augment accumulation of FA intermediates and triglycerides but also increase oxygen demand and generation of reactive oxygen species (ROS), leading to cardiac damage. Interestingly, increasing FA uptake through overexpression of cardiac human lipoprotein lipase (LPL) (260) or FA transport protein (47), or augmenting FA oxidation through overexpression of cardiac peroxisome proliferator-activated receptor (PPAR)-α (79) or long-chain acyl CoA synthase (48), results in a cardiac phenotype resembling diabetic cardiomyopathy. Conversely, normalizing cardiac metabolism in diabetic animals reverses the development of cardiomyopathy (21, 272). Taken together, these studies strongly support the role of altered metabolism in the development of diabetic cardiomyopathy.

CARDIAC METABOLISM

Glucose Uptake and Oxidation

Under normal physiological conditions, glucose is one of the major carbohydrates utilized by the heart. Glucose metabolism is regulated through multiple steps, including uptake, glycolysis, and pyruvate decarboxylation (Fig. 1). Cardiac glucose uptake is dependent on the transmembrane glucose gradient and the content of sarcolemmal glucose transporters (GLUT1 and GLUT4) (132, 154, 189). GLUT1 has a more pronounced sarcolemmal localization and represents basal cardiac uptake. When compared with GLUT1, GLUT4 is the dominant transporter in the adult heart, and under basal conditions, a majority of this transporter is located in an intracellular pool (154). Its translocation from an intracellular compartment to the sarcolemmal membrane requires insulin (154). Other than recruiting GLUT to the sarcolemmal membrane, insulin also influences glucose transport through its regulation of GLUT gene expression (137, 183). It should be noted that GLUT-mediated glucose uptake could also be stimulated through insulin-independent mechanisms. For example, recent studies have demonstrated that AMP-activated protein kinase (AMPK) also promotes GLUT4 redistribution to the sarcolemmal membrane (143, 261).

Once inside the cardiomyocyte, glucose is broken down through glycolysis, a sequence of reactions that convert glucose into pyruvate. Phosphofructokinase-1 (PFK1), the enzyme that catalyzes the generation of fructose 1,6-bisphosphate from fructose 6-phosphate, is a rate-limiting enzyme controlling glycolysis (57, 202). PFK-1 is inhibited by low pH, high
intracellular citrate, or ATP and is activated by ADP, AMP, phosphate, and fructose 2,6-bisphosphate (57, 202, 228). Fructose 2,6-bisphosphate is formed from fructose 6-phosphate catalyzed by PFK-2 (110). Given that PFK-2 is phosphorylated and activated by hormones, such as insulin (25, 58) and glucagon (228) or kinases such as AMPK (109, 161), stimulation of PFK-2 through these mechanisms increases fructose 2,6-bisphosphate generation, activates PFK-1, and subsequently promotes glycolysis. In an aerobic heart, glycolysis contributes <10% of total ATP generated, with no oxygen consumption.

After glycolysis, the pyruvate generated has three destinations: carboxylation to oxaloacetate or malate, reduction to lactate, and most importantly, decarboxylation to acetyl-CoA. To be oxidized, pyruvate is transported into the mitochondria and decarboxylated to acetyl-CoA through pyruvate dehydrogenase (PDH), a multienzyme complex. PDH is phosphorylated and inactivated by pyruvate dehydrogenase kinase (PDK) (107, 258), which is inhibited by pyruvate and stimulated by high mitochondrial acetyl-CoA-to-CoA and NADH-to-NAD+ ratios (29, 104). Acetyl-CoA then enters the tricarboxylic acid cycle and is eventually broken down to H₂O and CO₂ for ATP generation. Oxidation of one glucose provides 30 ATP with 6 oxygen consumed, which combined with 2 glycolytic ATPs produces a phosphate-to-oxygen ratio of 2.58 ATP/oxygen atom. Although glucose is the focus in this review, other carbohydrates like lactate also make an important contribution toward cardiac energy generation (39). In fact, as greater lactate compared with glucose utilization is observed in the isolated working heart (119, 127, 148), the inclusion of lactate in the perfusion buffer is recommended in future studies.

FA Uptake and Utilization

When compared with glucose, FA is the preferred substrate and accounts for ~70% of ATP generated in an aerobic heart. FA metabolism includes multiple steps and can be regulated by both acute and chronic mechanisms, with or without modulation of gene expression (Fig. 2).

Lipoprotein lipase. Because the heart has limited capacity to synthesize and store FA, it relies on continuous exogenous supply. FA supplied to the heart from the circulation is from two sources: albumin-bound FA and triglyceride (TG)-rich lipoproteins. It should be noted that the molar concentration of FA in lipoprotein-TG is ~10-fold larger than FA bound to albumin (165). Lipoprotein lipase (LPL) is the key enzyme that hydrolyzes lipoproteins to release FA. Thus, when lipoproteins are hydrolyzed by LPL, a large amount of FA are released and are believed to be the principle source of FA supplied to the heart (14, 237). LPL is produced in cardiomyocytes and subsequently secreted onto heparan sulfate proteoglycan binding sites on the myocyte cell surface (33, 68, 70). From here, LPL is transported onto comparable binding sites on the luminal surface of coronary endothelial cells (193). At these sites, LPL hydrolyzes TG-rich lipoproteins, such as very-low-density lipoprotein (VLDL) and chylomicrons, to release FA. Perfusion of working hearts with VLDL or chylomicrons, in the absence or presence of FA, has revealed that, compared with chylomicrons, VLDL is a poor substrate for LPL (100). In addition, utilization of chylomicrons was inhibited by free FA, which failed to affect cardiac VLDL utilization (100). Given the important role that LPL plays in regulating FA delivery, alteration in its level is able to change FA delivery and subsequent oxidation. Indeed, overexpression of LPL in the heart or skeletal muscle accelerates FA uptake (141, 260). Conversely, tissue-specific knockout of LPL in the heart switches the cardiac substrate selection preference to glucose (12, 13). Other than hydrolysis by LPL, lipoproteins can also be transported into the cardiac tissue with help of the lipoprotein receptor, with VLDL uptake through this mechanism being more substantial compared with chylomicrons (178).

FA transporters. Although FA can translocate into the cell through passive diffusion across the plasma membrane, FA
uptake shows saturation kinetics and is inhibited by proteases (7, 158, 159, 230). Thus FA transporters are also likely required to support this process. In the heart, three FA transporters have been identified and these include CD36, FA transport protein (FATP), and FA binding protein plasma membrane (FABPpm) (157). Given that 55–80% of FA transport was protein (FATP), and FA binding protein plasma membranes have been identified and these include CD36, FA transport protein (FATP), and FA binding protein plasma membrane (FABPpm). FA is converted to fatty acyl-CoA, which is transported into the mitochondria through CPT1/CPT2.

Under normal conditions, 70–90% of the esterified FA that enters cardiomyocytes is oxidized for ATP generation, whereas 10–30% is converted to TG (228). The TG pool is not static, with lipolysis and esterification taking place continuously (240). In a normal heart, intracellular TG level is constant, indicating a balance of lipogenesis and lipidolysis (210). In situations where FA supply supercedes the cellular oxidative capacity, such as obesity or diabetes, intracellular TG accumulates and is associated with lipotoxicity (240). Although TG is unlikely to be a direct mediator of cell apoptosis, its augmented lipolysis expands fatty acyl-CoA levels, which may be a key factor mediating cell apoptosis (117, 240). Thus TG is often used as a marker of lipotoxicity.

**PPARs.** PPARs are a group of ligand-activated transcriptional factors belonging to the superfamily of nuclear receptors. They are activated by either natural ligands like FA or numerous pharmacological ligands (80). Once activated, PPARs form complexes with retinoid X receptors and bind to the promoter regions of a number of target genes that encode the proteins involved in controlling FA metabolism (76, 78). Through regulation of expression of these genes, PPARs mediate FA utilization at the transcriptional level. PPARs have three isoforms: PPAR-α, PPAR-β (or -δ), and PPAR-γ. PPAR-α is extensively expressed in tissues with high FA metabolism like the heart (17). Activated by elevated intracellular FA levels, PPAR-α promotes expression of genes that regulate FA oxidation at various steps, such as FA uptake and binding (LPL, CD36, and FA binding protein), FA esterification (ACS), and FA oxidation (carnitine palmitoyltransferase-1, acyl-CoA oxidase, long-chain acyl-CoA dehydrogenase, and very-long-chain acyl-CoA dehydrogenase) (76, 78, 111). Knocking out cardiac PPAR-α abolishes fasting-induced overexpression of FA metabolic genes and switches substrate selection from FA to glucose (140, 172). Overexpression of cardiac PPAR-α augments FA uptake and oxidation (77, 79). Taken together, PPAR-α is believed to be the primary regulator of FA metabolism in the heart. Similar to PPAR-α, PPAR-β
Activated by elevated intracellular FA (45), PPAR-β (or -δ) augments expression of a group of genes that promote FA utilization (63, 169). Cardiac-specific knockout of PPAR-β also decreases FA oxidative gene expression and FA oxidation (46). Although the targets of PPAR-α and PPAR-β are partially overlapping (169), their unique roles and interaction remains unclear in the heart. PPAR-γ, the third number of the PPAR family, is highly expressed in adipose tissue. Through promoting lipogenic gene expression, PPAR-γ controls lipogenesis. Loss and gain of function experiments have demonstrated that PPAR-γ is necessary for adipose tissue proliferation and differentiation (16, 238). In isolated cardiomyocytes, the expression of PPAR-γ is barely detectable (89), suggesting a limited direct role for this nuclear receptor in regulating cardiac metabolism. However, the ability of PPAR-γ agonists to normalize elevated plasma concentrations of glucose and FA in diabetic animals will have a profound indirect effect on cardiac metabolism.

AMP-activated protein kinase. As an energy sensor, AMP-activated protein kinase (AMPK) is activated following a rise in the intracellular AMP-to-ATP ratio (97). Once stimulated, AMPK switches off energy-consuming processes like protein synthesis, whereas ATP-generating mechanisms, such as FA oxidation and glycolysis, are turned on (96, 105). In heart and skeletal muscle, AMPK facilitates FA utilization through its control of acetyl-CoA carboxylase (ACC) (133, 134). As ACC catalyzes the conversion of acetyl-CoA to malonyl-CoA, AMPK by inhibiting ACC is able to decrease malonyl-CoA and minimize its inhibition of CPT-1, the rate-limiting enzyme-controlling FA oxidation. AMPK has also been implicated in FA delivery to cardiomyocytes through its regulation of the FA transporter CD36 (155). Additionally, results from our laboratory have demonstrated a strong correlation between activation of whole heart AMPK and increases in coronary lumen LPL activity (8). Interestingly, recent studies using transgenic mice with a dominant negative form of AMPK has demonstrated that the lack of AMPK does not affect cardiac metabolism under physiological conditions (209, 259). At present, it is unclear as to what compensatory mechanisms are activated following knockout of AMPK. Additionally, it is unknown whether overexpression of AMPK could affect cardiac lipid homeostasis and metabolism.

Malonyl-CoA decarboxylase. In addition to AMPK, malonyl-CoA decarboxylase (MCD) is also known to promote FA oxidation through its lowering of malonyl-CoA. MCD catalyzes the degradation of malonyl-CoA to acetyl-CoA, leading to reduction of malonyl-CoA (65). This action relieves the inhibition of CPT-1 by malonyl-CoA and favors FA oxidation. Recent studies have suggested that inhibition of cardiac MCD leads to accumulation of malonyl-CoA and reduced FA oxidation (66).

Interaction Between Glucose and FA Metabolism

Regulation of glucose and FA metabolism does not occur independently, and numerous studies have reported a “cross-talk” between the utilization of these substrates (Fig. 3) (199, 211, 233). Randle et al. (199) demonstrated that FA impairs basal and insulin-stimulated glucose uptake and oxidation, an event that is known as the “Randle cycle” (199). FA influences glucose utilization at multiple levels. Accumulation of FA impairs insulin-mediated glucose uptake through inhibition of insulin receptor substrate and protein kinase B (94, 115, 187). Accumulation of FA leads to augmented intracellular FA derivatives, such as fatty acyl CoA, diacylglycerol, and ceramide. These FA metabolites activate a serine kinase cascade, which involves protein kinase C-θ and IκB kinase-β (inhibitor of NF-κB kinase-β), leading to serine phosphorylation of IRS (129, 269). Serine phosphorylation of IRS-1 reduces tyrosine

![Fig. 3](image-url)
phosphorylation and interferes with its ability to phosphorylate and activate phosphatidylinositol 3-kinase and protein kinase B (206). Increased intracellular FA also activates PPAR-α. As a consequence, PPAR-α promotes the expression of genes involved in FA oxidation, as well as pyruvate dehydrogenase kinase-4 (PDK4), which is known to inhibit PDH and pyruvate flux (257). Moreover, increased acetyl-CoA-to-free CoA and NADH-to-NAD⁺ ratios caused by the high rate of FA oxidation are also known to activate PDK4, leading to inactivation of PDH (29, 104). Augmented acetyl-CoA-to-free CoA ratio also causes accumulation of citrate in the cytosol, which subsequently inhibits PFK and glycolysis (85, 175). Conversely, inhibition of FA oxidation through elevation of malonyl-CoA levels, or using pharmacological inhibitors, favors glucose oxidation.

ALTERATION OF CARDIAC METABOLISM DURING DIABETES

Changes in Plasma Substrates

Glucose and lipids are the major substrates affected by diabetes. Hyperglycemia is a consequence of decreased glucose clearance and augmented hepatic glucose production, whereas enhanced lipolysis in adipose tissue and higher lipoprotein synthesis in the liver dramatically increases circulating free FA and TG. Because glucose entry into the cell is largely dependent on insulin, whereas FA transport across plasma membrane does not require any hormone, the augmented circulating lipids increase FA delivery to the cardiomyocyte. With the increase of intracellular FA, cardiac tissue rapidly adapts to promote FA utilization. In addition to diabetes, augmentation of plasma lipids by fasting or intralipid-heparin infusion also increases cardiac FA oxidation (52, 266).

Under conditions where FA supply supercedes the oxidative capacity of the heart, the FA is converted to lipids like TG or ceramide, with an end result being lipotoxicity (272). In obese ZDF rats, lowering of plasma lipids with a PPAR-γ agonist reduced cardiac TG and ceramide and improved heart function (272). Overall, these studies suggest that alterations in plasma lipids may drive changes in cardiac metabolism. It should be noted that a recent study using 4-wk-old ob/ob and db/db mice demonstrated altered cardiac metabolism without any change in plasma substrates (30). Hence, in these genetic mice models, intrinsic changes in the cardiomyocyte, rather than changes in circulating substrates, initiate alterations in cardiac metabolism at this early time point.

Defects in Cardiac Carbohydrate Utilization

In the obese or diabetic heart, myocardial glucose utilization is compromised at several points. In noninsulin-controlled Type 1 diabetic animals, reduced GLUT gene and protein expression compromises cardiac glucose uptake and oxidation (34). In obese or Type 2 diabetic animals, although there is hyperglycemia and hyperinsulinemia, cardiac glucose uptake is reduced as a consequence of reduced GLUT4 protein and impaired insulin signaling (38, 266). With the use of ob/ob and db/db mice, a recent study (30) reported that cardiac glucose oxidation is reduced at 4 wk of age and was associated with increased FA oxidation. Interestingly, this lower glucose oxidation occurred before the onset of impaired insulin signaling in the heart and development of hyperglycemia. Thus this early reduction in glucose utilization is likely due to suppression by high FA oxidation rather than impaired cardiac-specific insulin signaling. In another study that used db/db mice at different ages, increased cardiac FA oxidation preceded the reduction in glucose oxidation (5). Higher FA oxidation increases citrate, which is known to inhibit PFK, the rate-limiting enzyme in glycolysis. Elevated intracellular FA is also known to increase PDK-4 expression, which phosphorylates and inhibits PDH. Finally, high rates of FA oxidation augment acetyl-CoA that inhibits PDH either allosterically or through activation of PDK.

When compared with animal models, the use of carbohydrates in the human diabetic hearts is more controversial. In Type 1 diabetic patients, decreased myocardial carbohydrate uptake is reported (15, 62). With the use of an euglycemic insulin clamp, another study (179) has shown that cardiac glucose uptake is normal in these patients, suggesting that insulin is the major limiting factor that influences cardiac glucose uptake and no cardiac-specific insulin resistance is evident, as observed in skeletal muscle. In Type 2 diabetes, cardiac expression of GLUT4 is compromised likely due to elevated FA (10). However, a number of studies have also reported that cardiac tissue from Type 2 diabetic patients respond normally to insulin and show regular glucose uptake, suggesting that myocardial insulin resistance is not a common feature of Type 2 diabetes (118, 160, 242). Interestingly, a recent study has suggested that impaired myocardial glucose uptake is only observed in Type 2 diabetic patients with hypertriglyceridemia, suggesting that myocardial insulin resistance in these patients is associated with hypertriglyceridemia and augmented plasma FA levels (168).

Cardiac lactate utilization is also compromised following diabetes. In STZ-induced Type 1 diabetes, cardiac utilization of lactate is reduced to a greater extent when compared with glucose oxidation (41, 42). Moreover, hearts from 12-wk-old ZDF rats also showed lower carbohydrate oxidation, and this was almost entirely due to a reduction in lactate rather than glucose oxidation (43, 250). The mechanisms that mediate the inhibition of lactate utilization are unclear but is likely independent of any alterations in lactate dehydrogenase or lactate transporter (41).

The shift of cardiac energy substrate utilization from carbohydrate to lipids increases the intracellular glycogen pool, probably through augmented glycogen synthesis, or impaired glycogenolysis, or a combination of both processes (103, 136, 167, 223). Emerging evidence indicates that glycogen, in addition to its role as energy storage, is also able to regulate metabolism. At least in skeletal muscle, accumulation of glycogen acutely alters glycogen synthesis and glucose metabolism (59, 120–122). Chronically, glycogen accumulation may also impair insulin signaling in skeletal muscle (121). Whether cardiac glycogen accumulation also influences insulin signaling and metabolism is unknown. In addition, recent studies have identified a glycogen-binding domain in the β-subunit of AMPK and suggests that this domain links AMPK and glycogen (108). Although an association between high glycogen levels and repressed AMPK activity in human and rat skeletal muscle have been documented (254, 255), it is still unclear whether glycogen is able to regulate metabolism through AMPK.
Alterations in FA Utilization

Utilization of FA by cardiac tissue increases following obesity and diabetes. This change occurs not only as a consequence of increased FA supply but also through an intrinsic adaptation/maladaptation to elevated FA (234, 267). It must be acknowledged that some studies have also observed a reduced, rather than augmented, FA oxidation in Zucker fatty or ZDF rats (266, 272). In human diabetic patients, obese women demonstrate increased FA utilization, associated with augmented cardiac oxygen consumption, and reduced cardiac efficiency (190). Moreover, elevated cardiac TG and increased expression of PPAR-α target genes have been observed in patients without ischemic heart disease, very similar to lipotoxic ZDF rat hearts (220).

Lipoprotein lipase. The amount of FA supplied to the heart through LPL is influenced by multiple factors, including LPL activity and plasma lipoprotein concentration and composition. The relative contribution of cardiac LPL activity to the delivery of free FA to the diabetic heart is inconclusive. Thus LPL immunoreactive protein or activity has been reported to be unchanged, increased, or decreased in the diabetic rat heart. In part, this variability between different studies could be due to the diversity in the rat strains used, the dosage of STZ used to induce diabetes, and the duration of the diabetic state (203). In addition, many of the above investigations utilized procedures that did not distinguish between functional (i.e., heparin-releasable component localized on capillary endothelial cells that is implicated in the hydrolysis of circulating TG) and cellular (i.e., non-heparin-releasable pool that represents a storage form of the functional enzyme) pools of cardiac LPL because cellular LPL activity or protein levels have largely been obtained using whole heart homogenates. Rodrigues et al. (203) have previously reported that in STZ (55 mg/kg)-induced moderate diabetic Wistar rat hearts, HR-LPL activity is significantly increased. Induction of more severe diabetes using 100 mg/kg STZ did not influence HR-LPL (203). In another study using hearts from 65 mg/kg STZ-induced diabetic rats, HR-LPL decreased and was associated with reduced VLDL-TG lipolysis (182). Acute treatment of these diabetic rats with insulin enhanced both HR-LPL and VLDL-TG lipolysis (182). In mouse models of diabetes, although there is no change of cardiac HR-LPL activity in either STZ or db/db hearts, utilization of chylomicron-TG increases (174). Hence, the mechanisms that control cardiac LPL during diabetes are complex and have yet to be completely resolved.

It should be noted that even though LPL may not change following obesity or diabetes, increased circulating lipoproteins through LPL cleavage could still elevate FA supply to the cardiac tissue. However, increased concentration could be offset by changes in lipoprotein composition or lipoprotein receptor number. Binding of lipoproteins containing apolipoprotein (apo) CII to LPL enhances lipolysis (181), whereas binding of lipoproteins containing apoCIII or apoE suppresses LPL activity (1, 2). A recent study has shown that overexpression of HDL-associated apo AV accelerates hydrolysis of TG-rich lipoproteins, indicating the importance of this apo lipoprotein in stimulating LPL (166, 188). O’Looney et al. (181) have shown that induction of diabetes by STZ changes lipoprotein composition, with reduced apoCII levels, leading to impaired VLDL-TG lipolysis. A recent study has reported that expression of VLDL receptor decreases following STZ-induced diabetes (116).

FA transporters. During obesity and diabetes, the high rate of FA uptake is facilitated by FA transporters, leading to augmented FA oxidation and TG storage. In STZ-induced diabetes, the increase in plasma membrane CD36 and FABPpm amplifies FA uptake, an effect resulting from increased CD36 and FABPpm protein expression (152). In Zucker fatty rats, without a change in total protein, permanent relocation of CD36 and FABPpm to the cardiomyocyte plasma membrane augments FA uptake (55, 56, 153). The mechanism for this permanent repositioning of FA transporters at the plasma membrane is still unknown. Interestingly, in young (4 wk) ob/ob or db/db mice, cardiac FA oxidation increases without any change in circulating substrates (30). Given that the high rate of FA oxidation requires coordinated FA uptake, augmentation of CD36-mediated FA supply is suggested to be involved in facilitating FA oxidation at this early stage of insulin resistance.

PPAR-α. As the principle regulator of cardiac FA metabolism, PPAR-α plays an important role in controlling FA oxidation during obesity and diabetes. Activation of this nuclear receptor in the heart has been reported in almost all obese or diabetic animal models, including STZ-induced diabetic rats, ZDF rats, and ob/ob and db/db mice (30, 79, 220). Given that FA and its derivatives activate PPAR-α, higher cardiac PPAR-α activity is always observed when circulating lipids are augmented (30, 171). Hence, in ob/ob and db/db mice, activation of PPAR-α, evidenced by elevated expression of its downstream targets, is only observed at 12 wk and is associated with augmented plasma lipid (30). A similar association between plasma lipids and PPAR-α is also seen in hearts from STZ-induced diabetic rats, with only chronic (6 wk) but not acute (4 days) diabetes demonstrating activation of PPAR-α (unpublished data). Interestingly, in acute STZ diabetes or 4-wk ob/ob or db/db mice, increased FA oxidation is observed even in the absence of any change in cardiac PPAR-α and its downstream targets, suggesting PPAR-α independent control of FA oxidation. Identification of these mechanisms requires further studies.

After activation, cardiac PPAR-α promotes the expression of a group of genes involved in various steps of FA oxidation. Simultaneously, activation of PPAR-α also reduces expression of genes involved in glucose uptake, glycolysis, and oxidation through direct or indirect mechanisms (77, 79). With the use of transgenic mice, a recent study (186) demonstrated that knocking out cardiac PPAR-α prevented suppression of GLUT4 expression and glucose uptake by elevated plasma FA and improved myocardial recovery from ischemia following STZ diabetes induction, high-fat feeding, or fasting. Taken together, activation of cardiac PPAR-α not only favors FA oxidation but also inhibits glucose uptake and utilization, leading to augmented susceptibility to ischemic damage.

MCD. In STZ-induced diabetes, overexpression of cardiac MCD protein was observed and could contribute to the high rate of FA oxidation (213). It is unknown whether MCD also plays a role in augmenting cardiac FA oxidation in obese and Type 2 diabetes. Nevertheless, given that PPAR-α increases MCD expression (138, 265), higher MCD protein levels are expected following PPAR-α activation during obesity and Type 2 diabetes.
Limitations of Metabolic Measurements Using Radiolabeled Substrate

The majority of metabolic data in the above studies were obtained by using radiolabeled substrate perfusion of isolated hearts. In these methods, \(^{3}H\)glucose and \(^{14}C\)glucose were used to evaluate glycolysis and glucose oxidation, whereas \(^{3}H\)FA or \(^{14}C\)FA was used to estimate FA oxidation by measuring the generation of \(^3\)H\(_2\)O and \(^{14}C\)O\(_2\). Although this measurement allows for the manipulation of substrate concentration, there are limitations. First, the substrates used in perfused hearts do not truly reflect what the heart receives in vivo. For example, lipoproteins, lactate, and ketone bodies that are important substrates for the heart in vivo are rarely used to examine metabolism in perfused hearts. In addition, most metabolic data of diabetic hearts are obtained by using normal concentrations of glucose and/or palmitate, which differ from the elevated concentrations seen in the diabetic conditions in vivo. Another drawback is that diabetic hearts always have an elevated intracellular TG pool. Augmented intracellular TG turnover in diabetic hearts could dilute utilization of exogenous radiolabeled palmitate oxidation, resulting in an underestimation of FA oxidation (180). Finally, hormonal effects on energy metabolism are usually not considered (20), and lack of hormones in the in vitro perfusate may contribute to functional abnormalities that are not recapitulated in intact models.

CONSEQUENCES OF ALTERED METABOLISM IN DIABETIC HEARTS

Impaired Cardiac Function

Emerging evidence supports the concept that alterations in metabolism contribute toward cardiac contractile dysfunction. In STZ-induced diabetes, a larger number of studies have implicated metabolic abnormalities (FA oxidation provides almost 100% of ATP, with a dramatic decrease of glucose utilization) in cardiac contractile dysfunction (219, 227, 234, 267). In these animals, contractile failure begins as diastolic dysfunction, followed by severe systolic dysfunction (196, 219). Normalizing energy metabolism in these hearts reverses the impaired contractility (40, 176, 248). Animal models of obesity and Type 2 diabetes also exhibit cardiac dysfunction associated with altered cardiac metabolism (5, 21, 218). Some studies have observed both impaired diastolic and systolic function (3, 218), whereas other studies argue that no change in systolic function is present (6, 18, 164, 197). This discrepancy could be due to the severity of diabetes or the methods used to evaluate cardiac function. In diabetic patients, left ventricular hypertrophy and impaired isovolumic relaxation and ventricular filling are the most common abnormalities diagnosed (196).

During diabetes, changes in cardiac metabolism occur early and precede the development of cardiomyopathy. For example, in STZ-induced diabetes, altered cardiac metabolism is observed as early as 4 days following diabetes induction (88), whereas evidence of cardiomyopathy is only apparent after 4–6 wk. Similarly, in ob/ob and db/db mice, changes in cardiac metabolism are evident much before confirmation of cardiac dysfunction (5, 30). To validate the role of altered metabolism in provoking cardiac dysfunction, several studies have treated 6- or 9-wk-old db/db mice with either PPAR-\(\alpha\) or PPAR-\(\gamma\) agonists for 3–6 wk (3, 4, 36). Even though these treatments normalized cardiac metabolism, they failed to improve cardiac function in these mice, suggesting that metabolism may be unrelated to heart failure or that the treatment was not initiated in time. Interestingly, when ZDF rats were treated with a PPAR-\(\gamma\) agonist at 6 wk of age [when insulin resistance compared with 6-wk-old db/db mice is milder (37)], improvements of cardiac metabolism and heart function were observed (272). In a different study, changing cardiac metabolic profile by treating ZDF rats with PPAR-\(\gamma\) agonist also improved contractile function (91). Additionally, overexpression of GLUT4 in \(db/db\) mice not only normalized cardiac metabolism but also improved heart function (21, 218). These studies suggest that acute changes in metabolism likely induce early and reversible damage to cardiac tissue. Even though these early alterations are inadequate to produce cardiac functional changes, early interventions would be favored to provide protection against development of cardiomyopathy in the later stages of the disease.

The role of abnormal cardiac metabolism in cardiac dysfunction is also supported by studies using transgenic mice. Overexpression of cardiac PPAR-\(\alpha\) increased FA uptake and oxidation (79). The hearts from these transgenic mice exhibit a metabolic phenotype similar to diabetic hearts (79). Measurement of heart function revealed systolic dysfunction and ventricular hypertrophy in these hearts, indicating that, in the absence of systemic metabolic disturbances, alteration of cardiac metabolism is sufficient to induce cardiac contractile dysfunction (79). This concept is further substantiated by transgenic mice overexpressing cardiac ACS, FATP1, or LPL (47, 48, 260). These transgenic mice have shown increased FA uptake, utilization, or lipid accumulation, and these changes correlated well with contractile dysfunction.

In contrast, several studies have reported that altered metabolism has no impact on contractile function (224, 250). It should be noted that, in these studies, heart function was evaluated using a Langendorff heart perfusion. Given that diabetic hearts exhibit reduced mitochondrial oxidative capacity and cardiac efficiency (28, 106), it is possible that with increased workload and energy requirement, cardiac function would be compromised.

In addition to heart dysfunction per se, diabetic patients also have a greater incidence and severity of angina and acute myocardial infarction (147). After a myocardial infarction, diabetic patients have almost twice the rate of mortality compared with nondiabetics (229). Alterations in myocardial energy metabolism during diabetes are probably an important contributing factor in explaining this increased susceptibility to ischemic damage. In obese or diabetic animals, increased ischemic damage is also observed (5, 60, 93, 147), and normalization of cardiac metabolism in hearts from these animals has been shown to improve functional recovery following ischemia-reperfusion (147, 224, 270). Interestingly, a number of studies have also reported contradictory results, with decreased susceptibility to ischemia-reperfusion damage being reported in STZ or ZDF hearts (145, 150, 236, 249). Although the mechanisms for this observation are still unclear, decreased glycolysis and glycolytic products, a lower Na\(^+\)/Ca\(^{2+}\) activity, and a decreased clearance of protons via the Na\(^+\)/H\(^+\) exchanger have been proposed to explain this inconsistency (75).
Although changes in metabolism have been implicated in diabetic cardiac dysfunction, the mechanisms responsible are still unclear. Several factors have been proposed, and these include changes in Ca\(^{2+}\) homeostasis, decreased cardiac efficiency, lipotoxicity, and myocardial mitochondrial damage (Fig. 4).

**Effects on Ca\(^{2+}\) Homeostasis**

Within the cell, enzymes that catalyze glycolysis are located close to the sarcoplasmic reticulum and sarcolemma (71, 251), and ATP generated through glycolysis is preferentially used by ion transporters [like Ca\(^{2+}\)-ATPase (SERCA2a) and Na\(^+\)-K\(^+\)-ATPase] in these membrane fractions (71, 228, 252). Thus inhibition of cardiac glycolysis by high rates of FA oxidation during obesity and diabetes may impair intracellular Ca\(^{2+}\) handling (22). In other studies, a decrease in the activity of SERCA2a and Na\(^+\)/Ca\(^{2+}\) exchanger has been observed in Type 1 (99, 126) and Type 2 diabetic animals (22). Although the mechanisms for this reduction in gene expression are unclear, several studies have suggested that accumulation of glucose metabolites due to dissociation of glucose influx and pyruvate oxidation plays a role (51). Conversely, decreasing glucose metabolites has been shown to prevent the decrease in SERCA2a following diabetes (207). In other studies, a decrease in the activity of SERCA2a and Na\(^+\)/Ca\(^{2+}\) exchanger, without any change in expression or protein levels, have also been documented (215, 271). Irrespective of the mechanism, suppression of SERCA2a and the Na\(^+\)/Ca\(^{2+}\) exchanger results in poor calcium handling associated with impaired heart function (6, 22, 49). Interestingly, overexpression of SERCA2a in the diabetic heart improved Ca\(^{2+}\) handling (243) and cardiac function (239).

**Decreased Cardiac Efficiency**

When compared with glucose, oxidation of FA consumes more oxygen (2.58 vs. 2.33 ATP/oxygen atom). Cardiac efficiency, the ratio of cardiac work to myocardial oxygen consumption, changes with the type of substrate. Thus, in perfused hearts, provision of FA decreases cardiac efficiency compared with when glucose is the sole substrate (31, 162, 245). Additionally, decreased cardiac efficiency is also observed in human or experimental animals with obesity or diabetes (106, 162, 191). This reduction in cardiac efficiency and increased oxygen demand makes the heart especially vulnerable to damage following increased workload or ischemia. Interestingly, even though oxidation of FA requires 10% more oxygen compared with glucose, cardiac oxygen consumption is over 30% higher in ob/ob or db/db mice compared with control hearts, suggesting that other mechanisms also contribute to higher oxygen consumption and lower cardiac efficiency (37). A recent study reported oxygen wasting for noncontractile purposes in the diabetic heart (106). The mechanisms for this oxygen wasting are unknown, and uncoupled proteins (UCPs) are suggested as a potential target. In hearts from STZ-induced diabetic rats and ob/ob and db/db mice, augmented gene expression or protein levels of UCP2 or UCP3 have been reported (30, 102, 170, 171, 268). Other studies demonstrate no association between change in cardiac UCP protein levels and the onset of cardiac inefficiency (28, 30). Hence, additional studies are required to identify the targets that cause oxygen wasting observed in hearts from obese and diabetic animals.

**Lipotoxicity**

A number of studies have suggested that excessive FA overload induces lipotoxicity and contributes to the initiation and development of cardiomyopathy (194, 272). With the use of transgenic mice, studies have shown that elevation of FA uptake or utilization induces lipotoxicity in the absence of any systemic metabolic disturbance. Cardiac-specific overexpression of LPL or FATP1 significantly increased FA delivery with ensuing lipid storage, lipotoxic cardiomyopathy, and contractile dysfunction (47, 260). Moreover, elevating FA utilization by cardiac-specific overexpression of PPAR-\(\alpha\) or ACS also causes cardiomyopathy and cardiac dysfunction, similar to that seen during diabetes (48, 79). Conversely, reducing FA supply or utilization prevented the development of cardiomyopathy in obese or diabetic animals. In ZDF or transgenic mice with cardiac overexpression of LPL, a PPAR-\(\gamma\) agonist decreased plasma and cardiac intracellular lipids and ameliorated cardiomyopathy (244, 272). A recent study also demonstrated that increasing lipoprotein excretion by overexpressing human apoB reduced cardiac lipids and improved cardiomyopathy (264). Taken together, these studies provide convincing evidence that augmented FA supply during obesity or diabetes impairs cardiac lipid homeostasis and leads to lipotoxicity cardiomyopathy.
Although limited evidence is available of the existence of lipotoxicity in human diabetic patients, some studies have documented similarities between rodent lipotoxicity and the human metabolic syndrome (240). In a subgroup of patients with heart failure, Sharma et al. (220) have identified severe metabolic dysregulation characterized by intracellular TG accumulation and alterations in gene expression, similar to the lipotoxic rat heart. Increased apoptosis was also detected in ventricular biopsies from Type 2 diabetic patients (82). Additionally, cardiac PCr-to-ATP ratio was decreased in Type 2 diabetic patients and correlated well with plasma FA concentrations (216).

The mechanisms that mediate cardiac lipotoxicity are still not completely understood. One potential target is over production of ROS (79). High rate of FA oxidation increases mitochondrial action potential, leading to augmented ROS generation. Under normal physiological conditions, ROS is removed by cellular antioxidants. In the event of excessive generation of ROS, as observed in STZ-induced diabetic rats, ZDF rats, and db/db mice (19, 32, 272), it causes cardiomyocyte cell damage and augmented apoptosis. Another potential mechanism for lipotoxicity is accumulation of lipids, when FA uptake supercedes its oxidation. Regarding accumulation of TG, the role of this neutral lipid in inducing contractile dysfunction is still unknown, although a strong association between TG storage and lipotoxicity has been established in both animal models and human studies (50, 220, 272). Interestingly, a recent study suggested that TG formation actually provides protection against the deleterious effects of fatty acyl-CoA (144). Besides TG, excessive FA also leads to ceramide generation, an intracellular messenger known to trigger apoptosis (272). Accumulation of ceramide has been found in ZDF rats (272) or in isolated cardiomyocytes incubated with high fat (67, 101). Ceramide upregulates inducible nitric oxide synthase through activation of NF-κB, leading to increased generation of nitric oxide and peroxynitrite (241, 272). As a highly reactive molecule, peroxynitrite causes opening of the mitochondrial permeability transition pore and release of cytochrome c. Additionally, ceramide directly interacts with cytochrome c, leading to its release from the mitochondria (87). As a consequence, caspase is activated, which initiates the apoptotic pathway in cells. Additionally, with the use of isolated cardiomyocytes, high FA impairs cardiolipin and leads to ceramide-independent cell apoptosis (184). Finally, accumulation of FA metabolites has also been associated with insulin resistance. FA derivatives, such as fatty acyl CoA, diacylglycerol, or ceramide may activate a serine kinase cascade, which involves protein kinase C-δ and IκB kinase-β (inhibitor of NF-κB kinase-B), leading to serine phosphorylation of IRS (44, 114, 128, 129, 269). Following this, tyrosine phosphorylation of IRS and its ability to activate phosphatidylinositol 3-kinase and protein kinase B are compromised (206). Future studies are required to substantiate the roles of these FA derivatives in the development of insulin resistance, especially in the heart.

**Mitochondrial Dysfunction**

Mitochondria are the primary source of energy generation within cells. Acetyl-CoA generated from FA β-oxidation or glycolysis is used by the tricarboxylic acid cycle for production of NADH and FADH2. These electron carriers transfer electrons to the mitochondria electron transport chain, where ATP is ultimately generated. Thus cardiac mitochondrial dysfunction is expected to induce deleterious cellular effects, ultimately leading to heart disease. Indeed, humans with inherited or acquired mitochondrial defects develop cardiomyopathy (112, 208). With the use of transgenic mice models, mitochondrial dysfunction is also associated with heart disease. For instance, knock out of Ant1 (which controls exchange of mitochondrial ATP with cytosolic ADP) or Tfam (a mitochondrial transcription factor that regulates mitochondrial biosynthesis and gene expression) results in a cardiac energy deficit and cardiomyopathy (92, 142). Mice with cardiac-specific deletion of mitochondrial genes involved in FA oxidation also display a cardiomyopathic phenotype (72, 135). Interestingly, the opposite is also true with overexpression of PPAR-α (which regulates the expression of mitochondrial enzymes involved in FA oxidation) (79) or PGC1 (which controls mitochondrial biosynthesis) (139) resulting in mitochondrial dysfunction and cardiomyopathy. In Type 1 or Type 2 diabetic
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rats, impaired mitochondrial function has been demonstrated (222, 262), an observation similar to hearts from transgenic mice. Given the similarity between transgenic mice and models of diabetes, these studies strongly suggest that impairment of mitochondrial function contributes to the development of cardiomyopathy.

The mechanisms by which mitochondrial dysfunction contributes toward cardiomyopathy are still unclear. One potential target is ROS. Augmented ROS generation following high FA oxidation induces oxidative stress and cell damage. Inhibition of ROS by overexpression of metallothionein, MnSOD, or catalase has been shown to protect against mitochondrial dysfunction and cardiomyopathy (221, 262, 263). Another target is ceramide, through inhibition of mitochondrial respiratory chain, or inducing cytochrome c release from mitochondria and apoptosis, is suggested to provoke the development of cardiomyopathy (67, 95). Augmented expression of PGC1 in hearts from obese or diabetic animals may increase mitochondrial proliferation, mitochondrial ultrastructural abnormalities and dysfunction, and ultimately cardiomyopathy (139). Finally, following end stage diabetes, dysfunction of mitochondria causes energetic starvation, leading to heart failure (208).

**Summary**

In this review, we document that both insulin resistance and Type 1 and Type 2 diabetes exhibit similar alterations in cardiac metabolism through extrinsic and intrinsic mechanisms. The predominant change is a suppression of cardiac glucose utilization and a switch to excessive FA utilization associated with lipid storage. It should be noted that, in the majority of these studies, metabolic outcomes were obtained using ex vivo perfused working hearts. Additionally, only two substrates (glucose and fatty acid) were present in the perfusion buffer, and lactate, lipoproteins, ketone bodies, and relevant hormones were excluded. Hence, cardiac metabolism measured through this method may not reflect the in vivo situation. Despite these drawbacks, many studies have documented a strong correlation between altered cardiac metabolism and cardiac dysfunction observed during insulin resistance or diabetes. This correlation was further substantiated using transgenic mice with lipid oversupply in the absence of systemic interference. Regarding heart function, both diastolic and systolic dysfunction are observed in Type 1 diabetic animals. This is likely a consequence of prolonged hypoinsulinemia and hyperglycemia. With Type 2 diabetic models, there are conflicting reports, with some studies documenting both impaired systolic and diastolic function, whereas other studies argue against a change in systolic function. It is possible with Type 2 diabetic models, this discrepancy could be due to the severity or duration of hyperinsulinemia, and eventual hyperglycemia, or the techniques used to measure cardiac function. Finally, during diabetes, changes in cardiac metabolism occur early and precede the development of cardiomyopathy. Even though altered metabolism is inadequate to produce cardiac functional changes at this early time, it is likely that early metabolic damage is occurring at the cellular or subcellular levels. Over-time, these cumulative defects could be contributing to diabetic cardiomyopathy. Identification of this early damage could facilitate proper interventions and provide protection against development of diabetic cardiomyopathy in the later stages of the disease.

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