Loss of Lipoprotein Lipase-derived Fatty Acids Leads to Increased Cardiac Glucose Metabolism and Heart Dysfunction* 

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Long-chain fatty acids (FAs) are the predominant energy substrate utilized by the adult heart. The heart can utilize unesterified FA bound to albumin or FA obtained from lipolysis of lipoprotein-bound triglyceride (TG). We used heart-specific lipoprotein lipase knock-out mice (hLpL0) to test whether these two sources of FA are interchangeable and necessary for optimal heart function. Hearts unable to obtain FA from lipoprotein TG were able to compensate by increasing glucose uptake, glycolysis, and glucose oxidation. HLP0 hearts had decreased expression of pyruvate dehydrogenase kinase 4 and increased cardiomyocyte expression of glucose transporter 4. Conversely, FA oxidation rates were reduced in isolated perfused hLpL0 hearts. Following abdominal aortic constriction expression levels of genes regulating FA and glucose metabolism were acutely up-regulated in control and hLpL0 mice, yet all hLpL0 mice died within 48 h of abdominal aortic constriction. Older hLpL0 mice developed cardiac dysfunction characterized by decreased fractional shortening and interstitial and perivascular fibrosis. HLP0 hearts had increased expression of several genes associated with transforming growth factor-β signaling. Thus, long term reduction of lipoprotein FA uptake is associated with impaired cardiac function despite a compensatory increase in glucose utilization.

Normal cardiac muscle function requires adequate delivery of oxygen and energy substrates for the production of ATP. In the adult heart, fatty acid (FA) oxidation accounts for 60–70% of oxygen consumption, with the balance provided by glucose and lactate (1–3). However, during conditions such as ischemia (4, 5) and hypertrophy (4–6) the heart becomes more dependent on glucose. This initial adaptive response is beneficial in that it maintains ATP levels (7, 8) in the face of diminished mitochondrial oxidative phosphorylation. High rates of FA oxidation inhibit glucose oxidation and impair the recovery of mechanical function during reperfusion of ischemic hearts (9), whereas partial inhibition of FA oxidation during acute ischemia increases glucose oxidation and improves contractile power and efficiency (10–12). Several pharmacological agents have been developed, including dichloroacetate and ranolazine, which increase glucose oxidation in isolated hearts subjected to ischemia (4, 12). Furthermore, trimetazine, an inhibitor of long-chain 3-ketoacyl-coenzyme A thiolase (the final enzyme in the β-oxidation pathway), is cardioprotective in several models of ischemia (13). However, the long term effects of reduced FA oxidation on cardiac energetics and function are unknown.

All tissues have several routes through which they may acquire FAs. The heart avidly utilizes FA associated with albumin, and this can be demonstrated both in vivo and in perfused hearts. However, esterified FAs contained in lipoproteins are the major source of cardiac FA (14). These two sources of FA can compete for uptake in perfused hearts (15); it is not surprising, because conversion of TG to FAs along the endothelial surface should lead to high local concentrations of newly created free FAs. Whether the lipoprotein-derived FA and albumin-associated FA are interchangeable and can fully compensate for each other is unclear. Moreover, how the heart adjusts to chronic loss of FA-derived energy is also unknown.

Herein we report the effects of loss of local lipolysis on cardiac metabolism and function. Although steps involved in free FA metabolism were not altered, hearts from heart-specific lipoprotein lipase (LpL) knock-out mice (hLpL0) had reduced FA utilization and increased glucose oxidation. This was associated with increased expression of GLUT4 in cardiomyocytes, and decreased expression of PDK4. Despite minimal changes in expression of FA oxidation genes, FA oxidation rates were reduced in isolated perfused hLpL0 hearts. HLP0 hearts subjected to aortic banding, to assess the effects of altered substrate utilization on the development of cardiac hypertrophy, were unable to respond to stress. HLP0 hearts from older mice had diminished ejection fraction and extensive cardiac fibrosis. Thus, decreased availability of lipoprotein-derived FA in the heart leads to impaired cardiac function and contractility despite increased glucose utilization.

MATERIALS AND METHODS

Generation of Mice with Heart-specific Deletion of the Murine Lpl Gene—Genotypes were identified from tail tip DNA by PCR analysis as previously described (16, 17). Mice termed hLpL0 express the cre recombinase transgene, and both alleles are positive for the floxed Lpl gene. Mice termed wild-type contain neither the cre recombinase trans-
gene nor the floxed Lpl gene. All animals were maintained on a 12-h light-dark cycle and fed a chow diet.

**Heart and Plasma Lipids, FA, and Glucose**—We collected blood from 6-h-fasted 4- to 5-month-old mice (n = 10). Heart lipids were extracted as described by Folch et al. (18). Heart and plasma TG, cholesterol, FA, and glucose were measured enzymatically as described previously (19).

**LpL Activity**—LpL activity in homogenized tissues was measured as described by Hoquet et al. (20).

**In Vivo Kinetic Studies**—In vivo labeling of [3H]VLDL was performed as described (21). [14C]Palmitate (PerkinElmer Life Sciences) was complexed to 6% FA-free bovine serum albumin (Sigma) as described (22). We injected fasted hLpL0 (n = 5) and wild-type mice (n = 5) intravenously with 1 × 10^6 cpm of [3H]VLDL and 333,000 cpm of [14C]palmitate-bovine serum albumin and collected blood at 0.5, 1, 2, and 5 min after injection. Five minutes after injection, we perfused the body cavity with 10 ml of PBS by cardiac puncture and excised tissues.

**In Vivo Assessment of Cardiac Glucose Metabolism**—Basal glucose uptake was measured in hearts following an intravenous administration of 3 μCi of 2-deoxy-d-[1-14C]glucose (PerkinElmer Life Sciences). Blood was collected 2, 5, 15, 30, and 60 min following injection. At 60 min, hearts were perfused with PBS, tissues excised, and radioactive counts measured.

**Substrate Metabolism in Isolated Working Mouse Hearts**—Cardiac metabolism was measured in hearts isolated from 4- to 5-month-old male and female wild-type and hLpL0 mice (n = 5 per genotype). All hearts were prepared and perfused in the working mode, using protocols that have been previously described (23–26). In brief, the working heart buffer was Krebs-Henseleit buffer containing (in mM) 118.5 NaCl, 25 NaHCO3, 4.7 KCl, 1.2 KH2PO4, 2.5 CaCl2, 0.5 EDTA, and 5 glucose, gassed with 95% O2/5% CO2, and supplemented with 0.4 mM palmitate bound to 3% bovine serum albumin in the absence of insulin.

Glycolytic flux was determined by measuring the amount of 3H2O released from the metabolism of exogenous [5-3H]glucose (specific activity, 42 GBq/mol). Cardiac glycogen was digested with 0.5 mg/ml collagenase (Roche Applied Science) isolated from cardiomyocytes using TRIzol reagent, and gene expression was quantified by real-time PCR.

**Echocardiography**—Two-dimensional echocardiography was performed on conscious 4- and 6-month-old male and female (n = 10 per group) mice using techniques described previously (27). Two-dimensional echocardiographic images were obtained and recorded in a digital format. Images were then analyzed off-line by a single observer blinded to the murine genotype (28, 29).

**Isolation of Cardiomyocytes**—The hearts were excised from anesthetized mice and quickly connected to a Langendorff perfusion system. Hearts were perfused with calcium-free Hanks’ balanced salt solution (Invitrogen) at 37 °C and at a flow rate of 3.0 ml/min for 5 min. Hanks’ balanced salt solution buffer was gassed with 95% O2-5% CO2. Heart tissue was digested with 0.5 mg/ml collagenase (Roche Applied Science) in Hanks' balanced salt solution for 20 min. Digested ventricular tissue was removed and agitated to separate the cells. Cardiomyocytes were pelleted by low speed centrifugation at 180 × g for 1 min. DNA was isolated from cardiomyocytes using TRIzol reagent, and gene expression was quantified by real-time PCR.
5'-TGATCGGGTTCTAAGAC-3' and antisense 5'-ACGCTAGAGAGCATGTG-3'; and β-actin, sense 5'-GACGTTGACATCGTAAAAG-3' and antisense 5'-CAGTAAACAGTGCCGCT-3'.

**Histology**—Hearts from 4-month-old male mice were perfused with 10% buffered formalin solution. Hearts were subsequently immersed in 10% buffered formalin for 24 h and embedded in paraffin, and 5-μm sections of the ventricles were cut. Sections were stained with Masson’s Trichrome to assess interstitial fibrosis.

**Statistics**—Data are presented as means ± S.E. Isolated working heart data were analyzed by analysis of variance, and significant differences were evaluated by the Fisher Least Protected Squares test. Reverse transcription-PCR gene analysis data were non-normally distributed and were evaluated using the Mann-Whitney U test. Other comparisons were evaluated using the Student t-test.

**RESULTS**

Substrate Metabolism and Cardiac Power in Isolated Working Hearts—Albumin-bound FA oxidation should not directly be altered by loss of LpL. To determine if reduced supply of TG-derived FA altered substrate utilization by the heart, rates of glycolysis, glucose oxidation, and palmitate oxidation were measured in isolated working hearts. hLpL0 hearts from both 4- to 5-month-old male and female mice exhibited higher rates of glycolysis and glucose oxidation than control hearts (Fig. 1, A and B). In addition, palmitate oxidation rates in male and female hLpL0 hearts were reduced by 52 and 40%, respectively (p < 0.0001) (Fig. 1C). Thus, LpL-deficient hearts develop altered substrate utilization with increased reliance on glucose. The reduction in FA utilization could reflect a primary defect in FA oxidative capacity or could be secondary to increased glucose utilization (reverse Randle phenomenon). Thus albumin-associated FA is unable to compensate for loss of TG lipolysis. Male, but not female, hearts also had a significant reduction in cardiac power (Fig. 1D).

Metabolic Changes in Female hLpL0 Mice—Alterations in genes that regulate FA metabolism are often associated with more pronounced phenotypes in male animals, and in some cases no metabolic abnormalities are found in females (32, 33). We therefore assessed cardiac gene expression in female mice and, as shown in Fig. 2 (A and B), we noted reduced expression of PDK4 and acyl-CoA oxidase in these mice. This change would be expected to increase glucose utilization by reducing the phosphorylation of pyruvate dehydrogenase, which increases the activity of this key regulator of mitochondrial glucose oxidative flux. In contrast, the expression of CPT-1 and CD36, other genes involved in FA oxidation, were reduced and GLUT4 was increased, but not significantly. GLUT4 protein, by Western blot, was also increased (Fig. 2C). There was no change in PPARα and VLDL receptor expression (not shown). These changes support the hypothesis that the reduction in FA utilization due to LpL deletion could lead to increased glucose utilization.

Plasma Lipids and Glucose in Female hLpL0 Mice—We next studied TG, FA, and glucose metabolism in vivo. Four-month-old female hLpL0 mice (n = 10) had significantly elevated plasma TG compared with control (n = 10, 199 ± 24 mg/dl versus 71 ± 12 mg/dl, p < 0.001). However, plasma cholesterol, free FA, and glucose levels did not differ between the two groups: cholesterol 102 ± 16 versus 93 ± 13 mg/dl, glucose 121 ± 11 versus 131 ± 9 mg/dl, free FA 0.69 ± 0.06 versus 0.59 ± 0.07 mM (hLpL0 versus wild type). These findings are similar to the plasma lipid profile previously described in male hLpL0 mice (17). Thus, loss of heart LpL alone leads to increased plasma TG, an effect that is similar in both males and females.

The effects of cardiac LpL gene ablation on lipid and glucose uptake into female hLpL0 hearts were also assessed in vivo. LpL deletion led to a >80% reduction in cardiac LpL activity (Fig. 3A). TG-labeled VLDL and albumin-bound FA uptakes were assessed over 5 min; this allowed us to determine heart accumulation of [14C]palmitate and [3H]TG-VLDL prior to any recycling of the labels (19). Heart uptake of [3H]VLDL TG was decreased by 49% in hLpL0 female mice (n = 5, Fig. 3B). Loss of TG-derived FA should increase labeled palmitate uptake in vivo, as the competing unlabeled FAs from TG lipolysis are eliminated. hLpL0 heart uptake of [14C]palmitate was increased by 56% in hearts
from female hLpL0 mice (Fig. 3C). Myocardial basal uptake of 2-deoxy-D-[1-14C]glucose increased 5.5-fold (Fig. 3D). Thus, hLpL0 had increased uptake of glucose and free FA but reduced TG uptake in vivo.

**Cardiac Function in hLpL0 under Basal Conditions and following AbAC**—Although young mice exhibited no apparent cardiac dysfunction, echocardiography of 6-month-old mice revealed significant changes in cardiac function in both male and female hLpL0 mice. Male hLpL0 mice had increased left ventricular systolic dimension (Fig. 4A) and a 49% reduction in fractional shorting (Fig. 4B). Female hLpL0 also exhibited a 32% decrease in fractional shorting. Thus, the echocardiographic findings were consistent with impaired cardiac contractility. hLpL0 hearts had increased expression of markers of heart failure. Both male and female hearts exhibited increased expression of BNP compared with controls (Figs. 2 and 4C). SERCA2a mRNA levels were decreased in hearts from both male and female hLpL0 mice compared with controls (Fig. 4D). Taken together these changes in gene expression are consistent with deterioration in cardiac function. Paralleling the less severe metabolic changes, hearts from females were less severely affected.

4- to 5-month-old male hLpL0 mice were subjected to AbAC. Surprisingly, all banded hLpL0 mice (n = 5) died within 2 days; all control mice (n = 5) survived. To determine what might have led to this sudden death, we assessed cardiac function and gene expression in hearts 24 h after AbAC was performed. The increase in left ventricular systolic pressure was greater in hLpL0 hearts than in banded controls (Fig. 5A), and the left ventricular end diastolic pressure was significantly increased in banded hLpL0 hearts but not in banded wild-type hearts (Fig. 5B).

The expression of several genes involved in energy metabolism and heart function was altered in hearts from wild-type and hLpL0-banded mice (Fig. 6). This included increases in CPT1, myosin heavy chain-B, and SERCA2a, a protein involved in calcium re-uptake and muscle relaxation. PDK4 was reduced more in hLpL0 than wild-type hearts. This suggests that hLpL0 hearts had an even greater reliance on glucose oxidation than did hearts from wild-type mice. The increase in CPT1, a regulator of mitochondrial β-oxidation, should have led to greater utilization of FA in the wild-type hearts. However, because of the defective generation of FA in the hLpL0 hearts, this gene change might have been futile. Thus, hearts from hLpL0 mice are incapable of maintaining normal heart function in response to stress. This suggests that an optimal level of FA oxidation is required, along with greater glucose utilization, for the heart to respond to pressure overload.

To confirm that hLpL0 hearts had an alteration in energy stores, hearts from four control and hLpL0 male mice were used for ATP and...
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pCr measurements. pCr was 43 ± 3 nmol/liter/mg in control hearts and 28 ± 5 in hLpL0 hearts (p < 0.05). ATP levels did not differ; therefore, the pCr/ATP ratio was lower in hLpL0 than wild-type hearts (0.64 ± 0.07 versus 1.50 ± 0.10, p < 0.05).

Histological Changes in hLpL0 Hearts—Hearts from non-stressed 4- to 5-month-old male hLpL0 mice had increased fibrosis as indicated by Trichrome staining; a similar degree of fibrosis was not found in the females. The pattern of fibrosis was both interstitial and perivascular (Fig. 7). HLP0 hearts had increased expression of several genes involved in collagen deposition and matrix remodeling, including TGF-β, connective tissue growth factor, TIMP-1, matrix metalloprotease-2, and pro-collagen 1a4 (Fig. 8).

Gene Expression in Isolated Cardiomyocytes—To determine if gene expression changes observed in whole heart RNA preparations reflected changes in cardiomyocytes, cardiomyocytes were isolated from male hearts by perfusion with collagenase digestion and gene expression was examined. We observed a robust increase in the expression of GLUT4 (9-fold) in isolated cardiomyocytes (Fig. 9). Male hearts have a relatively greater increase in GLUT4 than female ones (17), and we suspect that changes in the composition of the hearts (a greater fibroblast to cardiomyocyte ratio in the impaired hLpL0 mice) was in part responsible for the more robust differences found with isolated cells. GLUT1, CD36, and PDK4 expression in cardiomyocytes was not changed. Thus, the marked increase in glucose uptake by hLpL0 hearts likely reflects increased uptake via GLUT4 transport. TSP-1 and TGF-β1 expression were also increased in the cardiomyocytes, implicating a role for the TGF-β pathway in the increased fibrosis observed.

DISCUSSION

The constant mechanical work of the heart requires a steady supply of energy primarily by the oxidation of FA. The source of these FAs could either be albumin-bound FA or FA liberated from lipoprotein TG. High rates of FA oxidation are thought to be detrimental to cardiac function as observed in the diabetic and ischemic heart (9, 34). This has led to the notion that increasing glucose oxidation and reducing FA oxidation is beneficial to the stressed heart. By using a model in which cardiac conversion of lipoprotein-TG to free FA was eliminated we demonstrated the importance of the LpL pathway for the long-term maintenance of cardiac FA utilization and the importance of FA oxidation for normal heart function. Our studies demonstrate the following: 1) Loss of LpL-mediated FA uptake by the heart was associated with significantly decreased cardiac FA oxidation rates, whereas rates of glucose oxidation and glycerolysis were markedly elevated. 2) HLP0 hearts had decreased expression of PDK4, and GLUT4 expression was markedly increased in cardiomyocytes. 3) In female mice, reduced FA oxidation was accompanied by reduced expression of some FA oxidation genes. 4) HLP0 hearts were unable to respond to aortic constriction. Energy stores in these hearts, as assessed by pCr, were reduced. Thus, a critical level of FA uptake and metabolism may be required for hearts to respond to acute pressure overload. 5) Contractile dysfunction and cardiac fibrosis was observed in hLpL0 hearts, and this was associated with increased cardiac expression of pro-collagen and TIMP-1.

The heart, like most tissues, obtains FA from several sources. Elimination of cardiomyocyte expression of LpL would be expected to markedly reduce heart uptake of lipoprotein-derived FA. Indeed, uptake of VLDL-TG was reduced by ~50% in female hLpL0 hearts. More than 90% of circulating FAs are esterified, and less than 10% are as free FAs (14). Surprisingly when hLpL0 hearts were studied in vitro, using a perfusate containing glucose and albumin-bound palmitate, oxidation of free FA was reduced. Thus, reduction in uptake of lipoprotein-derived FA leads to metabolic re-programming in the heart such that glucose utilization is increased and FA oxidation is decreased. A likely mechanism for this is reduced expression of PDK4 leading to increased activity and flux through pyruvate dehydrogenase, and increased expression of GLUT4 leading to increased glucose uptake in vivo and increased rates of glycolysis in isolated hearts. Paradoxically, in vivo palmitate uptake
was enhanced, presumably because competition of this tracer with TG-derived unlabeled FA was reduced. Nevertheless, the working heart data suggest that, despite increased free FA uptake, oxidation of albumin-associated FA is reduced \textit{in vivo}. It should be noted that both the mechanical and metabolic effects found in the isolated working heart experiments were less remarkable than those found \textit{in vivo}. This is expected as the fuel sources used \textit{in vitro}, glucose and free FA, effectively bypass LpL, and their use would be expected to eliminate on-going LpL-mediated metabolic deficiencies.

Other potential routes of lipoprotein-derived fatty acid uptake, including via members of the LDL receptor superfamily, proteoglycans, scavenger receptors, and other lipases, are also bypassed in the perfused heart. However, it should be noted that our \textit{in vivo} data show that none of these other routes are sufficiently important to compensate for the loss of LpL.

Although young mice, 2 months old, had normal cardiac function, to our surprise, at 6 months, both male and female hLpL0 mice exhibited diminished cardiac function. Left ventricular fractional shorting was significantly decreased in hLpL0 hearts compared with wild type. Moreover, the expression of several heart failure markers was altered; BNP was increased. A reduction in SERCA2a as well as the down-regulation of \(\alpha\)-major histocompatibility complex may also have contributed to the cardiac dysfunction in the hLpL0 hearts.

It is widely believed that increasing glucose oxidation and decreasing FA oxidation in the stressed heart is beneficial in maintaining cardiac contrac-
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Our present findings suggest that chronic adaptations leading to increased myocardial glucose utilization and decreased FA utilization could be deleterious in the long term.

To test this hypothesis, AbAC was performed on 4- to 5-month-old wild-type and hLpL0 mice to induce cardiac hypertrophy. Unexpectedly, 100% of hLpL0 mice died within 2 days while all banded wild-type mice continued to thrive. We assessed cardiac function and gene expression in hearts banded for 24 h to determine what might have led to the sudden death. Cardiac catheterization suggested that hLpL0 mice were somewhat more impaired functionally than banded wild types. Although differences measured at 24 h were not large, we believe that these studies assessed acute and not chronic events. Our present findings suggest that chronic adaptations leading to increased myocardial glucose utilization and decreased FA utilization could be deleterious in the long term.

In contrast to models in which the reduction in FA oxidative capacity is greater than a reduction in FA uptake such as PPARα knock-out mice treated with a FA oxidation inhibitor (37), hLpL0 mice do not develop a lipid-associated dilated cardiomyopathy. Tissue-specific PPARβ knock-out mice also developed a lipotoxic cardiomyopathy (38). Both PPARα and PPARδ modulate cardiac lipid oxidation; however, a detailed analysis of FA uptake versus oxidation has not yet been performed in these knock-out models. Chronic use of FA oxidation inhibitors also leads to diastolic dysfunction associated with increased cardiac lipid (39). In contrast, defective FA utilization in hLpL0 hearts occurs on the basis of reduced uptake and oxidation of FA. Thus, the pathophysiology of cardiac dysfunction in hLpL0 mice is not complicated by a superimposed lipotoxicity.

Our observations resemble, in part, those reported from the cardiac insulin receptor knock-out mouse model (40). Isolated perfused hearts from these mice have increased glucose uptake and glycolysis. Hearts from 16- to 20-week-old mice had decreased palmitate oxidation and a modest decrease in cardiac function. Furthermore, these hearts had increased injury and contractile dysfunction after aortic constriction (41). Transgenic mice overexpressing human GLUT4 also have increased cardiac glycolysis (23), but cardiac function in older GLUT4 transgenic mice and with stress has not been reported. GLUT1 transgenic mice have greater glucose...
up to no evidence of cardiac dysfunction, and increased survival after ascending aortic constriction (42). FA utilization by these hearts was not reported. Thus differences in the route of glucose uptake, the degree of glucose oxidation, or the ability to also increase FA uptake during stress allows GLUT1 transgenic hearts, unlike the hLpL0 hearts, to provide additional energy needed for pressure overload hypertrophy.

Histological analysis revealed interstitial and perivascular fibrosis in hLpL0 hearts. Cardiac fibrosis is due to increased extracellular matrix deposition by myofibroblasts. Several factors cause fibrosis in the heart, including hormones of the renin-angiotensin system, growth factors, and inflammatory cytokines such as TGF-β (43). TGF-β is thought to be the central mediator of the fibrotic response. We measured the gene expression of several downstream targets of TGF-β and observed increased expression of connective tissue growth factor, TIMP-1, and pro-collagen 1.

We observed a modest increase in the expression of TGF-β in hearts from hLpL0 mice; the activity of this cytokine is primarily post-translationally regulated (44). Increased activity of TGF-β up-regulates the expression of numerous profibrotic proteins in the heart (45), lung (46), and liver (47). The mRNA levels of both TGF and TSP-1 were increased in isolated cardiomyocytes. TSP-1 is a major activator of TGF-β (48). It is unclear whether the fibrosis results from reduced FA uptake or greater glucose utilization. Moreover, our data do not identify the primary dysfunctional cell, myocytes, or myofibroblasts.

In summary, we show that mice with defective FA utilization due to loss of TG lipolysis in the heart have increased glucose oxidation and develop cardiac dysfunction. These data confirm that free FAs are unable to substitute for lipoprotein-derived FA in vivo. Moreover, although several acute models suggest that reduced FA oxidation may be beneficial in stressed hearts, in the present study, hearts that were chronically dependent on glucose had an age-related decline in cardiac contractility associated with fibrosis. These hearts were unable to adapt acutely to pressure overload induced hypertrophy. The mechanisms for this are not entirely clear, but we postulate that adaptive hypertrophy requires both glucose and FA. In conclusion, our studies demonstrate that the heart has an optimal balance between use of glucose and FA. Chronically altering this balance may lead to cardiac dysfunction.

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