Chylomicron and palmitate metabolism by perfused hearts from diabetic mice

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Submitted 26 August 2002; accepted in final form 15 October 2002

FATTY ACIDS (FA) are generally considered to be the preferred oxidative substrate for the heart (41). The two sources of FA for cardiac metabolism are 1) circulating FA bound to plasma albumin that can be taken up directly by the heart, and 2) hydrolysis of triacylglycerols (TG) in circulating chylomicrons by endothelium-bound lipoprotein lipase (LPL) provides a source of fatty acids (FA) for cardiac metabolism. The effect of diabetes on the metabolism of chylomicrons by perfused mouse hearts was investigated with db/db (type 2) and streptozotocin (STZ)-treated (type 1) diabetic mice. Endothelium-bound heparin-releasable LPL activity was unchanged in both type 1 and type 2 diabetic hearts. The metabolism of LPL-derived FA was examined by perfusing hearts with chylomicrons containing radiolabeled TG and by measuring 3H2O accumulation in the perfusate (oxidation) and incorporation of radioactive activity into tissue TG (esterification). Rates of LPL-derived FA oxidation and esterification were increased 2.3-fold and 1.7-fold in db/db hearts. Similarly, LPL-derived FA oxidation and esterification were increased 3.4-fold and 2.5-fold, respectively, in perfused hearts from STZ-treated mice. The oxidation and esterification of [3H]palmitate complexed to albumin were also increased in type 1 and type 2 diabetic hearts. Therefore, diabetes may not influence the supply of LPL-derived FA, but total FA utilization (oxidation and esterification) was enhanced.

Chylomicrons are the preferred lipoprotein substrate for LPL (14). Recently, chylomicron metabolism has been measured with isolated perfused working hearts from rats (15, 42) and mice (29), so that the metabolic fate of LPL-derived FA could be compared with the utilization of albumin-bound FA.

Metabolism of exogenous substrates is altered markedly in diabetic hearts (26, 38). As a consequence of decreased glucose utilization and increased oxidation of albumin-bound FA by hearts from insulin-deficient (type 1) diabetic rats (35), FA oxidation becomes almost the exclusive energy source for the diabetic hearts. Similar results showing elevated FA oxidation have been reported recently for perfused working hearts from diabetic db/db mice (2), an animal model of type 2 diabetes with obesity and insulin resistance (9, 22). However, observations that FA oxidation was increased in type 1 and type 2 diabetic hearts have been obtained from perfusions with albumin-bound FA (palmitate) only (2, 35, 38). In the case of chylomicron metabolism, the supply of FA for the diabetic heart could be altered if endothelium-bound LPL activity is changed, in addition to potential alterations in the metabolic fate of LPL-derived FA. Endothelium-bound (functional) LPL can be displaced into the perfusate of ex vivo hearts by heparin (6). Therefore, the first objective of this investigation was to determine whether heparin-releasable LPL (HR-LPL) activity was changed in hearts from diabetic mice by use of genetic type 2 diabetic db/db mice as well as streptozotocin-induced insulin-deficient type 1 diabetic mice. The second objective was to assess the metabolic fate of LPL-derived FA in diabetic hearts (oxidation, esterification to intracellular TG) from perfusions with radiolabeled chylomicrons (29). Comparative experiments on the metabolism of an albumin-bound FA (palmitate) were conducted with perfused hearts from diabetic mice.

METHODS

Diabetic mouse models. Genetically diabetic C57BL/KsJ-lepr<sup>db</sup>/lepr<sup>db</sup> (db/db) type 2 diabetic mice and lean control heterozygotes (db/+) were purchased from Jackson Laboratories (Bar Harbor, ME). All experiments were conducted on male animals at 12 wk of age, when plasma insulin levels in db/db mice are at peak values with concomitant hyperglycemia (2, 9).

A chemically induced murine model of insulin-deficient type 1 diabetes was also utilized. Swiss Webster (SW) male mice (30–40 g) were acquired from local breeding sources provided by the University of Calgary. Mice (10 wk of age)
were treated with streptozotocin (STZ), which produces selective necrosis of pancreatic β-cells, resulting in a well-characterized model of insulin deficiency that has been used to evaluate changes in cardiac function (39). STZ was prepared in 100 mM citrate buffer (pH 4.5) at a concentration of 30 mg/ml and was administered to animals by intraperitoneal injection over a 3-day protocol (18). On the 1st day, mice received 85 mg/kg STZ, on the second day 70 mg/kg, and on the third day 55 mg/kg, for a total cumulative dose of 210 mg STZ/kg mouse body weight. Control animals received only the citrate buffer. Metabolic studies were conducted 2 wk after the 3-day STZ injection protocol (at 12 wk of age). Insulin-deficient (type 1) diabetes was also produced by administration of STZ to C57BL/KsJ-lepr/c mice, which also have an insulin deficiency that has been used as a model of type 2 (lepre) diabetes (30). Rates of FA oxidation were determined from the hydrogen production of working heart perfusion, and the generation of 3H2O was measured, as described in the preceding section on CM-[3H]TG metabolism. Parameters of contractile function were measured every 15 min.

Statistics. Results are presented as means ± SE. An unpaired t-test was used to test for significant differences be-

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between control and diabetic hearts; a $P$ value < 0.05 was considered significant.

RESULTS

Characteristics of control and diabetic mice. Type 2 diabetic $db/db$ mice were markedly obese and hyperglycemic (Fig. 1) relative to control heterozygotes ($db/+), consistent with previous studies (2). Induction of insulin-deficient (type 1) diabetes by administration of STZ to SW and $db/+$ mice produced an equivalent degree of hyperglycemia (Fig. 1; 30.1 ± 0.8 and 28.5 ± 1.4 mM glucose, respectively), but these diabetic mice lost weight (−5.1 ± 1.5 g and −8.5 ± 0.7 g, respectively) over the 2-wk treatment.
hearts (1,913 ± 0.7 g) and STZ-treated db/+ (19.8 ± 0.6 g) mice were significantly lower compared with control SW (39.2 ± 1.3 g) and db/+ (30.0 ± 0.7 g) mice. Heart weights were also reduced significantly in type 1 diabetic mice (Fig. 1); in contrast, heart weight was unchanged in type 2 db/db mice.

**Mouse heart LPL activity.** Perfusion of mouse hearts with heparin resulted in the rapid release of LPL activity into the perfusate, which then declined to preheparin levels by the end of the perfusion (Fig. 2). HR-LPL activity in the perfusate is the result of heparin displacing the enzyme from heparan sulfate proteoglycan-binding sites on the endothelial surface of the coronary vasculature (6, 14). The peak HR-LPL activity in the perfusate is the result of heparin-releasable lipoprotein lipase (Fig. 2); oxidation of LPL-derived FA by control SW and db/db hearts was significantly higher than by control hearts at all time points. When steady-state rates were calculated (mean of the three perfusion times), the oxidation of LPL-derived FA by db/db hearts (0.32 ± 0.04 μmol min⁻¹ g dry wt⁻¹) was 2.3-fold higher than the rate of oxidation (0.14 ± 0.02 μmol min⁻¹ g dry wt⁻¹) by control db/+ hearts (Fig. 3B).

The incorporation of radioactivity into tissue lipids was also measured (11, 29). Esterification to tissue TG was increased from 0.10 ± 0.02 μmol min⁻¹ g dry wt⁻¹ in db/+ hearts to 0.17 ± 0.03 μmol min⁻¹ g dry wt⁻¹ in db/db hearts (Fig. 3B). The percentage of incorporation of radioactivity into tissue TG relative to total lipid incorporation was 74 ± 1 and 80 ± 2% for db/+ and db/db hearts, respectively. There was also no difference between db/+ and db/db hearts for the low incorporation of radioactivity into other lipid classes.

When the fate of LPL-derived FA was calculated from the sum of oxidation and esterification rates (Fig. 3B), FA oxidation represented 58 ± 4 and 66 ± 2% of total FA utilization by control db/+ and diabetic db/db hearts. Thus, although total utilization (oxidation plus esterification) of LPL-derived FA was elevated in db/db hearts (0.49 μmol min⁻¹ g dry wt⁻¹) compared with db/+ hearts (0.24 μmol min⁻¹ g dry wt⁻¹), the relative proportion undergoing oxidation vs. esterification was unchanged.

**Chylomicron metabolism by perfused working mouse hearts.** Working mouse hearts were perfused with [³H]chylomicron with a TG concentration of 0.4 mM, chosen as representative of a postprandial concentration in vivo (29, 42). The fate of LPL-derived FA from CM-[³H]TG hydrolysis was determined by measuring the accumulation of ³H₂O in the perfusate (FA oxidation) and the incorporation of radioactivity into tissue lipids (esterification) at the end of the 90-min perfusion (11, 29). The time course of ³H₂O accumulation in the perfusate of db/+ and db/db hearts was reasonably linear (Fig. 3A); oxidation of LPL-derived FA by db/db hearts was significantly higher than by control hearts at all time points. When steady-state rates were calculated (mean of the three perfusion times), the oxidation of LPL-derived FA by db/db hearts (2,452 ± 177 nmol h⁻¹ mg⁻¹; n = 6).

![Fig. 2. Mouse heart lipoprotein lipase activity. Heparin-releasable lipoprotein lipase (HR-LPL) activity was measured in the perfusate from control db/+ (○; n = 10) and diabetic db/db (●; n = 10) hearts (A) and from control SW (○; n = 10), STZ-induced diabetic Swiss-Webster (SW/STZ, ▲; n = 9), and STZ-induced diabetic db/+ (db/+ (STZ), ▼; n = 6) hearts (B). For clarity, mean values only (not ±SE) are shown.](http://ajpendo.physiology.org/)
hearts was identical (Fig. 4A), consistent with similar HR-LPL activities (Fig. 2). The accumulation of $^{3}$H$_{2}$O in the perfusate of SW(STZ) hearts was higher than respective control rates at all perfusion times (Fig. 4A). Consequently, steady-state oxidation rates were increased from 0.13 ± 0.03 to 0.44 ± 0.09 μmol·min$^{-1}$·g dry wt$^{-1}$ by control SW and diabetic SW(STZ) hearts, respectively (Fig. 4B). A very similar rate of oxidation was observed for diabetic $db/+$ (STZ) hearts (0.44 ± 0.06 μmol·min$^{-1}$·g dry wt$^{-1}$), which was elevated significantly compared with control $db/+$ hearts (0.14 ± 0.02 μmol·min$^{-1}$·g dry wt$^{-1}$).

Esterification into tissue TG (Fig. 4B) was also elevated in SW(STZ) and $db/+$ (STZ) hearts (0.20 ± 0.04 and 0.18 ± 0.02 μmol·min$^{-1}$·g dry wt$^{-1}$, respectively) compared with control SW and $db/+$ hearts (0.08 ± 0.01 and 0.10 ± 0.02 μmol·min$^{-1}$·g dry wt$^{-1}$, respectively). Incorporation into tissue TG as a percentage of total lipid incorporation was 73 ± 2 and 77 ± 2% for SW(STZ) and $db/+$ (STZ) hearts, which was not different compared with SW (73 ± 2%) and $db/+$ (74 ± 1%) control hearts. The proportional fate of LPL-derived FA between oxidation and esterification was also calculated. FA oxidation was 69 ± 4 and 71 ± 4% of total FA utilization (oxidation + esterification) for SW(STZ) and $db/+$ (STZ) hearts, respectively, compared with 63 ± 7% for control SW and 58 ± 4% for control $db/+$ hearts. Thus, as noted for $db/db$ hearts, the enhanced total utilization (oxidation plus esterification) of LPL-derived FA by type 1 diabetic SW(STZ) hearts (0.64 μmol·min$^{-1}$·g dry wt$^{-1}$) compared with control SW hearts (0.21 μmol·min$^{-1}$·g dry wt$^{-1}$) was not associated with any change in the relative proportion undergoing oxidation vs. esterification. Finally, it is evident that there are no significant strain differences for chy-

![Figure 3](image3.png)

**Fig. 3.** Chylomicron metabolism by perfused working hearts from control $db/+(n = 4)$ and type 2 diabetic $db/db(n = 4)$ mice. Hearts were perfused with a 0.4 mM $[^{3}$H]chylomicron (CM) preparation. A: oxidation of lipoprotein lipase (LPL)-derived fatty acids (FA) was determined by measuring the perfusate content of $^{3}$H$_{2}$O for hearts from $db/+(•)$ and $db/db(○)$ mice at the indicated perfusion times. B: steady-state rates of LPL-derived FA oxidation and esterification were measured for control and $db/db$ hearts. Values are means ± SE. *P < 0.05 relative to $db/+$ control hearts.

![Figure 4](image4.png)

**Fig. 4.** Chylomicron metabolism by perfused working hearts from control and type 1 diabetic hearts. Hearts were perfused with a 0.4 mM $[^{3}$H]chylomicron preparation. A: oxidation of LPL-derived FA was determined by measuring the perfusate content of $^{3}$H$_{2}$O at the indicated perfusion times for hearts from control SW ($•; n = 6$), SW(STZ) ($•; n = 8$), control $db/+(•; n = 4$), and $db/+$ (STZ) ($○; n = 6$) mice. B: steady-state rates of LPL-derived FA oxidation and esterification. Values are means ± SE. *P < 0.05 relative to respective control hearts.
Lipid metabolism by perfused hearts from SW and db/db mice (±STZ).

Palmitate metabolism by perfused working mouse hearts. Previous publications have reported that palmitate oxidation was increased in perfused hearts from db/db mice (1, 2), but esterification was not measured. Therefore, in this study, db/db and db/+ hearts were perfused with albumin-bound [3H]palmitate. Palmitate oxidation by db/db hearts increased 3.9-fold, as observed previously (1, 2). Incorporation of radiolabeled palmitate into tissue TG was 0.10 ± 0.02 μmol·min⁻¹·g dry wt⁻¹ (n = 5) and 0.18 ± 0.03 μmol·min⁻¹·g dry wt⁻¹ (n = 4; P < 0.05) for db/+ and db/db hearts, respectively. Thus, both oxidation and esterification of palmitate were increased in db/db hearts, consistent with results for LPL-derived FA (Fig. 3). Palmitate metabolism was also studied with perfused hearts from type 1 diabetic mice. Palmitate oxidation was reasonably linear with perfusion time for control SW and db/+ hearts (Fig. 5A), with steady-state rates of 0.54 ± 0.11 and 0.47 ± 0.17 μmol·min⁻¹·g dry wt⁻¹ (Fig. 5B) that are very similar to previous results (2, 29). Rates of palmitate oxidation for diabetic SW(STZ) and db/+(STZ) hearts were more than doubled, to 1.12 ± 0.09 and 1.01 ± 0.09 μmol·min⁻¹·g dry wt⁻¹, respectively. Esterification to tissue TG was increased significantly in SW(STZ) hearts (0.25 ± 0.01 μmol·min⁻¹·g dry wt⁻¹) compared with control SW hearts (0.17 ± 0.03 μmol·min⁻¹·g dry wt⁻¹; Fig. 5B). In contrast, esterification to TG in db/+(STZ) hearts was not significantly different from that in control db/+ hearts. As observed for hearts perfused with CM-[3H]TG, the incorporation of radioactivity into TG after [3H]palmitate oxidation was determined from the perfusate content of 3H2O, at the indicated perfusion times, for hearts from control SW (●; n = 8), SW(STZ) (■; n = 8), control db/+ (□; n = 3), and db/+(STZ) (▲; n = 4) mice. B: steady-state rates of palmitate oxidation and esterification. Values are means ± SE. *P < 0.05 relative to respective control hearts.

Contractile function in perfused working mouse hearts. A number of contractile parameters were monitored at 15-min intervals during working heart perfusions. In general, cardiac function was stable over the 90-min perfusion for both control and diabetic hearts, with the exception that there was a progressive decline in heart rates for the type 1 SW(STZ) and db/+(STZ) hearts perfused with [3H]palmitate. Average values calculated from all time points are presented in Table 1 for hearts from db/+ and db/db (perfusions with chylomicrons) and SW and SW(STZ) mice (perfusions with both chylomicrons and palmitate). Heart rates for db/db and SW(STZ) hearts were significantly lower than for their respective controls, but all other parameters of contractile function were unchanged. Consequently, the rate-pressure product (HR × PSP), an accepted index of cardiac performance (42), was significantly reduced in db/db hearts (17.2 ± 0.4 mmHg/
min × 10⁻³; n = 4) and in SW(STZ) hearts (17.5 ± 0.4 mmHg/min × 10⁻³; n = 8) relative to respective control hearts (db/+; 19.7 ± 0.1 mmHg/min × 10⁻³; n = 4; SW, 19.4 ± 0.7 mmHg/min × 10⁻³; n = 6). Similar results were obtained with perfusions of db/+ (STZ) hearts with chylomicrons, except that cardiac output (6.4 ± 0.1 ml/min) was reduced significantly compared with control db/+ hearts (8.3 ± 0.1 ml/min; Table 1). However, the dry weight of db/+ (STZ) hearts was lower than that of control hearts (Fig. 1). When cardiac output was corrected for this difference in dry weight, cardiac output for diabetic db/+ (STZ) hearts (284 ± 5 ml·min⁻¹·g dry wt⁻¹) was no longer different from the cardiac output calculated for control db/+ hearts (296 ± 3 ml·min⁻¹·g dry wt⁻¹).

**DISCUSSION**

**Effect of diabetes on mouse heart LPL activity.** LPL is an endothelium-bound enzyme in the heart that hydrolyzes the TG core of circulating lipoproteins like chylomicrons, providing FA for uptake and metabolism by cardiomyocytes. Thus LPL has an essential role in the utilization of TG-rich lipoproteins as an energy source for the heart (6, 14). Therefore, the first objective of this investigation was to determine whether endothelial bound HR-LPL activity was changed in perfused hearts from diabetic mice.

Possible mechanisms that could change HR-LPL activity in diabetic hearts include 1) altered synthesis and/or processing of LPL in cardiomyocytes (6), 2) altered translocation from cardiomyocytes to functional sites on endothelial cells in the coronary vasculature (32), and 3) altered binding of LPL to the endothelium because of changes to heparan sulfate proteoglycans on the cell surface (10, 34). The influence of type 2 diabetes on cardiac LPL activity has not been investigated in detail. Although cardiac LPL activity in obese and insulin-resistant Zucker fatty rats has been reported to be either unchanged (27) or decreased (4), these studies did not measure functional endothelium-bound HR-LPL activity by a heparin perfusion protocol. Furthermore, HR-LPL activity has not been determined for hearts from Zucker diabetic fatty rats, another monogenic model of type 2 diabetes with obesity and insulin resistance (22). With perfused hearts from db/db mice, an accepted monogenic model of obesity and type 2 diabetes (9, 22), HR-LPL and residual tissue LPL activities were not different from activities in hearts from control db/+ heterozygotes or SW mice (Fig. 2). Although Kobayashi et al. (19) reported that LPL mRNA was reduced in hearts from db/db mice, this change in LPL gene expression must not be accompanied by any alteration in cardiac LPL activity. It should be noted that the absence of a change in HR-LPL activity in db/db hearts does not conflict with the observation that the hypertriglyceridemia in db/db mice (19) was due to reduced catabolism of TG-rich lipoproteins (23). First, endothelium-bound LPL could be reduced in other db/db tissues (adipose tissue, skeletal muscle) because of tissue-specific mechanisms that regulate LPL activity (6). Second, changes in the composition of the TG-rich lipoproteins (30) could reduce their catabolism in vivo without any change in LPL catalytic activity measured in vitro. And finally, an LPL inhibitor could be present in diabetic mice (20).

The effect of type 1 diabetes on cardiac LPL activity has been the subject of many more investigations, with discrepant results. Induction of insulin-deficient type 1 diabetes by STZ administration to rats has been associated with reduced (24, 29), unchanged (33), or increased (32, 36) cardiac HR-LPL activities. Differences in the duration and severity of STZ-induced diabetes and the influence of the rat strain (Sprague-Dawley, Wistar, Wistar Kyoto) contribute to this variability in responses of cardiac HR-LPL activity to type 1 diabetic conditions. In the present study, although there was a slight increase in peak HR-LPL activity (Fig. 2) in hearts from SW(STZ) and db/+ (STZ) mice, total HR-LPL activity, which will be the best reflection of endothelium-bound activity, was not different from total HR-LPL activities in control SW and db/+ hearts. It must be acknowledged that in vitro determinations of HR-LPL activity in postheparin perfusates may represent a maximal activity or capacity of LPL that may not necessarily reflect the in vivo activity of the endothelium-bound enzyme. Nevertheless, it is reasonable to conclude that neither type 2 diabetes (db/db mice) nor type 1 diabetes (STZ-treated SW and db/+ mice) has any effect on functional endothelium-bound cardiac HR-LPL or residual tissue LPL activities. In other words, the supply of LPL-derived FA from degraded chylomicrons by perfused hearts from diabetic mice will be unchanged. Thus uptake of FA may be dependent on factors other than LPL activity, in particular...
the metabolic needs of the heart. Therefore, perfusions of diabetic hearts with chylomicrons allowed us to examine whether the fate of LPL-derived FA was altered, which was the second objective of this investigation.

Chylomicron and palmitate metabolism by diabetic mouse hearts. Perfusions of hearts from db/db, SW-(STZ), and db/+ (STZ) mice with radiolabeled chylomicrons revealed that both the oxidation and esterification of LPL-derived FA were enhanced compared with control SW and db/+ heart perfusions (Figs. 3 and 4). Therefore, both type 2 and type 1 diabetic models result in enhanced cardiac utilization of LPL-derived FA. This influence of diabetes on the fate of LPL-derived FA, with an increase in both oxidation and esterification to tissue TG, was very similar to the fate of [3H]palmitate complexed to albumin. Belke et al. (2) reported previously that rates of palmitate oxidation were increased in db/db hearts. The elevated TG content of db/db hearts (1) is consistent with the increased FA esterification observed in the present study. In addition, [3H]palmitate oxidation and esterification by type 1 SW(STZ) and db/+ (STZ) hearts were increased relative to control hearts (Fig. 5). Therefore, although the absolute rates of FA utilization were much higher for [3H]palmitate compared with LPL-derived FA from CM-[3H]TG catabolism, the stimulatory effect of diabetes on FA utilization was the same, irrespective of the source. It must be acknowledged that this comparison of chylomicron and palmitate metabolism by diabetic mouse hearts was conducted with concentrations that reflect a control postprandial (fed) condition, when chylomicrons (0.4 mM TG) will be present and FA concentrations will be low (0.4 mM; see Ref. 2), because adipose tissue lipolysis will be suppressed under fed conditions. Future experiments should determine the metabolism of diabetic hearts perfused with elevated concentrations of chylomicrons and FA that reflect diabetic conditions.

A number of biochemical mechanisms could account for the increase in FA utilization by diabetic hearts. Increased FA oxidation could be due to upregulation of mitochondrial uncoupling proteins (5, 16) in diabetic mouse hearts. The content of uncoupling protein 3 was increased in hearts from STZ-treated rats (43). It should be noted that the observation of increased rates of FA oxidation in diabetic mouse hearts (Figs. 3–5) without any change in contractile function (Table 1) suggests that cardiac efficiency was reduced in diabetic hearts, which could be due to uncoupling of oxidative phosphorylation and reduced ATP synthesis in mitochondria from diabetic hearts due to increased content of uncoupling protein(s). A second unknown aspect of efficiency is whether β-oxidation intermediates accumulated in cardiac tissue during the perfusion time course. Another mechanism resulting in increased FA oxidation in diabetic mouse hearts could be enhanced entry of FA into mitochondria because of a reduction in the content of malonyl-CoA, an inhibitor of carnitine palmitoyltransferase-1 (35, 38).

Because esterification to tissue TG was also increased in diabetic mouse hearts along with enhanced FA oxidation, additional mechanisms must also contribute to the overall increase in FA utilization by diabetic mouse hearts. Increased FA utilization could be due to increased rates of FA uptake by diabetic mouse hearts as the consequence of an increased abundance of putative FA transporters in the plasma membrane (28).

The plasma concentrations of both TG-rich lipoproteins and FA-albumin are increased in both type 1 (17) and type 2 (19, 23) diabetic conditions in mice. The chronic overutilization of plasma lipids by diabetic hearts could contribute to the reduced mechanical function that constitutes a diabetic cardiomyopathy (13, 25, 37), perhaps as a consequence of a cardiac lipotoxicity mechanism (40, 44). Consistent with this proposed lipotoxicity mechanism are recent observations of the use of genetically engineered mice with enhanced cardiac FA utilization, due to cardiac-specific overexpression of either long-chain fatty acyl-CoA synthetase (8) or peroxisome proliferator-activated receptor-α (12), which exhibited reduced cardiac contractile function. Therefore, interventions that can reduce FA utilization by diabetic hearts will be an important goal for future investigations.

The expert technical assistance of Mariette Chuang is gratefully acknowledged.

This study was supported by an operating grant (MT 13227) from the Canadian Institutes of Health Research.

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