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A SWEET HEART: INCREASED CARDIAC GLUCOSE UPTAKE IN PATIENTS WITH LIPOPROTEIN LIPASE DEFICIENCY

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In the healthy adult human heart, 70% of the energy required for normal cellular function is derived from the uptake and oxidation of fatty acids, with the remainder being contributed by glucose, lactate and amino acids. Fatty acids are delivered to the heart either of two pathways: 1) free fatty acids (FFA) primarily originating in adipose tissue and associated with plasma albumin, and 2) fatty acids derived from lipoprotein lipase (LpL) mediated hydrolysis of lipoprotein triglycerides (TGs). The relative importance of each of these pathways in normal and pathological myocardial energy metabolism is unclear. Loss of the fatty acid uptake receptor CD36, which likely affects both sources of lipid uptake, leads to heart dysfunction in humans (1), but perhaps not in mice (2). In contrast, there are no reports of heart function in LpL deficient humans. It is possible that the heart either fully compensates for loss of LpL-derived fatty acids or that FFA, and not LpL mediated breakdown of lipoproteins, are the major source of heart energetic lipids. If this latter hypothesis were true, hearts from LpL-deficient humans would not need to alter their uptake of glucose.

¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) scanning has been used to quantify myocardial blood flow and metabolism in the normal state and in patients with left ventricular hypertrophy, atherosclerosis and dilated cardiomyopathy. In this study, we used FDG-PET scanning to characterize myocardial glucose uptake in two patients with LpL deficiency and compared them against a healthy control subject and a patient with heart failure.

Patient I was a 21-year-old female of French-Canadian descent with a history of a cholecystectomy and LpL deficiency. Her LpL deficiency was first documented during an episode of pancreatitis while on birth control pills and was confirmed by a reduction in post-heparin plasma LpL activity to less than 10% of normal. Her plasma TG level had been as high as 79.1 mmol/l (7000 mg/dl). Subsequently, she was treated with a fenofibrate and fish oil supplements. Three years later, with a plasma TG level of 33.1 mmol/l (3000 mg/dl), she suffered another episode of acute pancreatitis. Her diet and exercise were modified and she began to use medium chain TG oil. At the time of the FDG-PET study, her TG was 24.9 mmol/l (2205 mg/dl) and she had been pancreatitis free for more than a year.

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Disclosures:
None

Patient II was a 52-year-old female whose LpL deficiency was confirmed in childhood by hypertriglyceridemia and reduced post-heparin plasma LpL activity. As a young adult she had two episodes of pancreatitis after being on birth control pills. Prior to her scan, fasting TG was 3.36 mmol/l (2957 mg/dl) while on dietary restrictions.

The control patient was a healthy 52-year old male, while the patient with heart failure was a 55-year old male with non-ischemic cardiomyopathy.

Both LpL deficient patients and the control subject had normal cardiac function and none of the patients had diabetes.

In preparation for PET imaging, patients fasted overnight for at least 6 hours with baseline fasting blood glucose measured. For resting myocardial perfusion imaging, the patients received an intravenous bolus of 0.28 mCi/Kg of $^{13}\text{N-NH}_3$ with a simultaneous 2-D dynamic acquisition protocol (10 sec/frame $\times$ 12, 30 sec/frame $\times$ 2, 180 sec/frame $\times$ 1). One hour later, patients were injected with 10 mCi of $^{18}\text{F-FDG}$ and PET scanning began simultaneously, using a 2-D dynamic acquisition protocol over 60 minutes (10 sec/frame $\times$ 12, 30 sec/frame $\times$ 10, 120 sec/frame $\times$ 10, 300 sec/frame $\times$ 6). Heparin was not injected prior to the injection of $^{18}\text{F-FDG}$. Plasma glucose was measured 0, 15, 30 and 60 minutes after $^{18}\text{F-FDG}$ injection. All images were corrected for scatter and measured photon attenuation. Image reconstruction was performed using iterative reconstruction and a Butterworth filter. It should be noted that the appearance of the relatively larger left ventricle volumes relative to wall thickness in the perfusion images for the control subject are due to differences in the zoom factor used during the acquisition of images and not due to the presence of a dilated cardiomyopathy.

For quantitative analysis, the LV myocardium was divided into 5 regions of interest, (anterior, septal, apical, lateral and inferior). Time activity curves and input functions were generated for each region of interest and for the blood pool by placing a small region of interest within the basal LV blood pool on the mid-ventricular slice. A two compartment kinetic model was used to calculate myocardial blood flow in each region of interest using $^{13}\text{N-NH}_3$. Patlak analysis was used to calculate the rate of myocardial glucose uptake (MGU) from $^{18}\text{F-FDG}$ time activity curves for each region of interest, and globally for the LV. Mean MGU for the entire myocardium was calculated by averaging MGU values for all regions of interest.

Prior to FDG administration, fasting plasma glucose for patient I was 5.3 mmol/l (96 mg/dl) and for patient II was 5.6 mmol/l (102 mg/dl). FDG-PET scan from patient I revealed resting myocardial perfusion that was qualitatively (Figure 1a top row) and quantifiably normal (Table 1). FDG uptake was also clearly visible (Figure 1a bottom row) and quantifiable (Table 2), demonstrating a diffuse and marked increase in non-insulin stimulated FDG uptake in all myocardial segments compared to the control subject (Figure 1c). Mean MGU was 9-fold higher than control (Figure 1a), with the greatest MGU seen in the basal-lateral segments of the myocardium. FDG-PET images from patient II, secondary to mis-registration from patient motion, demonstrated a perfusion defect in the anterior and lateral walls of the myocardium with a similar reduction in FDG uptake in these regions. However, mean MGU in patient II (Figure 1b) was 7.2 fold higher than control, with MGU being greatest in the distal-anterior segments (Table 2). This increased FDG uptake by the hearts of LpL deficient patients was substantially greater than that seen in the patient with heart failure (Figure 1d), where MGU was more focal and patchy, demonstrating a 1.75 fold increase in the basal-anterior segments of the myocardium (Table 2), with a fasting plasma glucose of 9.2 mmol/l (94 mg/dl).

Our study demonstrates a marked and diffuse increase in cardiac glucose uptake in patients with LpL deficiency. The likely explanation for this is that the heart has compensated for loss of LpL-derived lipids as a source of energy by increasing glucose uptake and oxidation, implying that lipoprotein-derived fatty acids, and not just FFA, are a major source of cardiac energy. Animal models with heart-specific loss of LpL also demonstrate a marked increase in glucose uptake (3). Although heart failure patients have increased myocardial glucose uptake, our patients had normal heart function.

Increased myocardial FDG uptake is a metabolic feature of other conditions, such as myocarditis (4), sarcoidosis (5), endocarditis (6), acute myocardial ischemia (7), chronic hibernating myocardium and recent myocardial ischemia with delayed recovery of fatty acid metabolism (i.e. ischemic memory) (8, 9). Therefore a marked increase in glucose uptake is not pathognomonic for any of these conditions. As we demonstrate here, LpL deficiency may be another possible explanation for increased myocardial glucose uptake as detected by PET scanning.

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Fig 1.

FDG-PET resting myocardial metabolism images of the left ventricle. Short-axis views are provided for each patient. Top row contains $^{13}\text{N-NH}_3$ resting perfusion images of the left ventricle. Bottom row, are $^{18}\text{F-FDG}$ resting myocardial metabolism images of the left ventricle. One hour after infusing the IV bolus of $^{13}\text{N-NH}_3$, patients were injected with 10 mCi of $^{18}\text{F-FDG}$ and PET scanning began simultaneously using a 2-D dynamic acquisition protocol over 60 minutes. FDG uptake in the left ventricle of (a) LpL deficient patient I. Mean MGU = 122.3 ± 30.1 nmol/g/min, (b) LpL deficient patient II. Mean MGU = 98.1 ± 11.5 nmol/g/min, (c) control subject. Mean MGU = 13.6 ± 2.0 nmol/g/min, (d) heart failure patient. Mean MGU = 15.1 ± 5.4 nmol/g

Table 1

Mean blood flow (MBF)

Patient		Basal Anterior	Distal Anterior	Basal Inferior	Distal Inferior	Basal Septal	Distal Septal	Basal Lateral	Distal Lateral	Apex
LpL I	MBF (ml/kg/min)	0.89	0.87	0.76	0.84	0.79	0.78	0.64	0.65	0.75
LpL II	MBF (ml/kg/min)	0.76	0.74	0.72	0.64	0.73	0.79	0.65	0.62	0.67
Heart Failure	MBF (ml/kg/min)	0.58	0.54	0.45	0.47	0.57	0.58	0.44	0.46	0.35
Control	MBF (ml/kg/min)	0.76	0.82	0.84	0.86	0.90	0.88	0.66	0.64	0.68

Table 2

Myocardial glucose uptake (MGU)

Patient		Basal Anterior	Distal Anterior	Basal Inferior	Distal Inferior	Basal Septal	Distal Septal	Basal Lateral	Distal Lateral	Apex
LpL I	MGU (nmol/g/min)	139	144	121	136	128	126	149	46	112
LpL II	MGU (nmol/g/min)	105	114	94	104	102	105	96	75	88
Heart Failure	MGU (nmol/g/min)	28	10	16	12	14	17	16	12	11
Control	MGU (nmol/g/min)	16	14	12	13	15	16	14	12	10