Time Course of Alterations in Myocardial Glucose Utilization in the Zucker Diabetic Fatty Rat with Correlation to Gene Expression of Glucose Transporters: A Small-Animal PET Investigation

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Diabetic cardiomyopathy is associated with abnormalities in glucose metabolism. We evaluated myocardial glucose metabolism in a rodent model of type 2 diabetes, namely the Zucker diabetic fatty (ZDF) rat, and validated PET measurements of glucose uptake against gene and protein expression of glucose transporters (GLUTs). Methods: Six lean and ZDF rats underwent small-animal PET at the age of 14 wk and at the age of 19 wk. The imaging protocol consisted of a 60-min dynamic acquisition with 18F-FDG (18.5–29.6 MBq). Dynamic images were reconstructed using filtered backprojection with a 2.5 zoom on the heart and 40 frames per imaging session. PET measurements of myocardial glucose uptake (MGUp) rate and utilization were determined with an input function derived by the hybrid image–blood-sampling algorithm on recovery-corrected anterolateral myocardial regions of interest. After the PET session at week 19 (W19), hearts were extracted for gene and protein expression analysis of GLUT-1 and GLUT-4. The dependence of MGUp on gene expression of GLUT-1 and GLUT-4 was characterized by multiple-regression analysis. Results: MGUp in ZDF rats at both week 14 (W14) and W19 (P < 0.006) was significantly lower than MGUp in lean littermate control rats. Moreover, lean rats at W19 displayed significantly higher MGUp than they did at W14 (P = 0.007). Consistent with a diminished MGUp result, gene expression of GLUT-4 was significantly (P = 0.004) lower in ZDF rats. Finally, MGUp significantly (P = 0.0003) correlated with gene expression of GLUT-4. Conclusion: Using small-animal PET, we confirmed alterations in myocardial glucose utilization and validated PET measurement of MGUp against gene and protein expression of GLUTs in the diabetic heart of an animal model of type 2 diabetes.

Received Feb. 11, 2008; revision accepted Apr. 7, 2008.

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Heart disease is the leading cause of death among patients with diabetes (1,2). Increasing evidence suggests that patients with diabetes have a predisposition to heart failure resulting from impairment in heart muscle contraction, particularly abnormalities in diastolic function (3). This impairment in muscle contraction, termed diabetic cardiomyopathy, is independent of vascular abnormalities as diastolic dysfunction is evident in patients with both type 1 and type 2 diabetes (T2D). Several theories have been put forth that explain diabetic cardiomyopathy, including stiffness of the left ventricle (LV) due to an accumulation of connective tissue and insoluble collagen (4) and abnormalities in calcium flux (5). One prominent hypothesis argues that diabetic cardiomyopathy is a consequence of alterations in myocardial fuel metabolism (6,7).

The heart can use multiple substrates including fatty acids (FAs), carbohydrates, amino acids, and ketones (8). Under normal conditions, the heart generates 50%–70% of the energy it needs through FA oxidation, whereas glucose and lactate account for 30%–50% of energy provided to the cardiac muscle (9,10). In the diabetic heart, however, the contribution of glucose to total overall energy expenditure is diminished to the extent that the heart muscle relies exclusively on FA for energy needs (11). It has recently been demonstrated that normalizing cardiac metabolism in animals with diabetes reverses the development of cardiomyopathy (12). Thus, it is highly desirable to characterize
substrate utilization in vivo noninvasively in both human and animal models of diabetes as it would provide an avenue for staging both disease and efficacy of therapy.

PET has been used to quantify myocardial substrate use in humans (13–17) (reviewed in Herrero and Gropler (18) and Kudo (19)); however, small-animal PET of substrate use has been met with several challenges including partial-volume effects, extraction of the input function for the quantification of PET images, and, more generally, the validation of PET outcome measures. In a series of publications, we have characterized methods to extract the input function (20–22) and developed multiparameter small-animal PET quantification techniques (23) to assess myocardial blood flow (24) and substrate metabolism (25) as a proof of concept. In this article, we characterize myocardial glucose utilization (MGU) in an animal model of T2D, namely the Zucker diabetic fatty (ZDF) rat.

The ZDF rat is a well-characterized model for T2D, with obesity resulting from loss-of-function mutation in the leptin receptor and onset of diabetes at the age of 12 wk (26).

To characterize the time course of alterations in MGU, we noninvasively assess the myocardial glucose uptake rate (MGU up) and utilization in the ZDF rat and its lean littermate using small-animal PET in conjunction with 18F-FDG. Furthermore, we validate PET measures of glucose utilization both by virtue of the animal model and by correlation of PET measures of MGU up to gene and protein expression of glucose transporters (GLUTs), namely GLUT-1 and GLUT-4. In doing so, we demonstrate alterations in MGU in the diabetic heart. Furthermore, consistent with metabolic findings, gene and protein expression of GLUT-4 are markedly diminished in the heart of ZDF rats. Finally, we show that PET measures of 18F-FDG uptake rate correlate with gene and protein expression of GLUT-4.

MATERIALS AND METHODS

All chemicals, unless otherwise stated, were purchased from Aldrich Chemical Co., Inc. Radioactive samples were counted on an 8000 γ-counter (Beckman Coulter). Small-animal PET was performed on either the microPET Focus-120 (27) or Focus-220 (28) (Siemens Inc.).

Synthesis of Radiopharmaceuticals

18F-FDG is produced routinely in our laboratory with a commercially available module (CTI Molecular Imaging).

Animals Used in This Study

The study used 6 male ZDF rats (fa/fa) and 6 age-matched lean male littermates (fa+/+) (Charles River Laboratories) (Table 1). ZDF and lean littermates were fed Constant Nutrition 5008 (Purina), consisting of 26.8% protein, 16.7% fat, and 56.4% carbohydrates. With the abovementioned diet, ZDF rats are expected to develop diabetes by the age of 12 wk; however, they were initially scanned at the age of 14 wk, thus allowing 2 additional weeks for full onset of T2D.

Animal Preparation

Six hours before the imaging session, rats were fasted in metabolism cages while water was given ad libitum. On the day of the study, rats were anesthetized by inhalation of 2%–2.5% isoflurane administered via an induction chamber. Anesthesia was maintained throughout the imaging session by delivering 1%–1.5% isoflurane via a custom-designed nose cone. The rat’s neck was shaved and scrubbed in preparation for a sterile cut-down procedure. A 1- to 1.5-cm incision was made over the right jugular vein. The vein was exposed and ligated, and a MicroRenathane catheter (outer diameter, 0.025 mm, and inner diameter, 0.012 mm) (Braintree Scientific, Inc.) was sutured in place. Rats were globally heparinized (10 mg/kg) to prevent the catheter from clotting. Body temperature was maintained using a circulating water blanket and a heat lamp. Pediatric electrocardiograms lead (Red Dot Infant Electrodes; M.M.M. Co.) were placed on the rat’s hind limbs to measure and record heart rate. All animal experiments were conducted in compliance with the guidelines for the care and use of research animals established by the Animal Studies Committee of Washington University. Sharp et al. (23) provide a more detailed description of the animal-handling methodology.

Echocardiography (ECHO) Measurements

Noninvasive examination of the heart was performed using ultrasound (Vevo770 Ultrasound System; VisualSonics Inc.) at ages 13 and 18 wk according to the following procedures. Rats were anesthetized by continuous inhalation of 1% gaseous isoflurane administered via a customized nose cone and secured on an imaging platform in the supine position. Physiologic parameters including heart rate, respiratory rate, and core body temperature were continuously monitored by a built-in monitoring system. The anterior chest was shaved and ultrasonic coupling gel was applied. Ultrasound studies were performed using a transducer (16-MHz imaging frequency). Care was taken to maintain adequate contact and avoid excessive pressure on the chest. Complete 2-dimensional and M-mode examinations were performed from multiple views. Image analysis included standard ECHO parameters of left ventricular structure and systolic or diastolic function. In addition, measures of left ventricular structure were used for partial-volume corrections performed in conjunction with kinetic modeling.

Small-Animal PET Protocol

The animals were secured in a custom-designed acrylic restraining device and were placed inside the field of view of the small-animal imaging PET scanner. Five seconds after a bolus injection of the radiopharmaceutical via the right jugular catheter, dynamic PET image acquisition was started. Each rat was imaged at 2 different times: once at the age of 14 wk and again at the age of 19 wk. The imaging protocol consisted of a 60-min dynamic acquisition with 18F-FDG (18.5–29.6 MBq) to characterize glucose utilization. During each imaging session, 5–6 whole-blood arterial samples were collected from the femoral artery to measure whole-blood glucose (5 μL), free fatty acid (FFA) (20 μL), and insulin (5 μL) levels. Finally, heart rates were recorded at baseline and throughout the study. Dynamic images were reconstructed using filtered backprojection with a 2.5 zoom on the heart and 40 frames per imaging session.

Substrate Analysis

All substrate measurements were performed using commercially available, well-documented methods that have been validated in small animals (23). Briefly, whole blood (20–25 μL) was drawn into a precision disposable micropipette (Wiretrol II; Drummond Scientific Co.) for insulin and FFA analysis. The blood was spun in a
microcentrifuge (13,460g for 2 min) to separate red blood cells and plasma. The plasma was immediately placed in a 280°C freezer until analyzed. FFA levels were measured using a standard Nefa-C kit (Wako Chemicals USA Inc.) by the Diabetes and Metabolism Core Laboratory of the Washington University School of Medicine (WUSM), Department of Endocrinology. Insulin levels were measured using a rat insulin ELISA test kit (Crystal Chem, Inc.) by the Developmental Biology Core Laboratory of the WUSM, Department of Pediatrics. Plasma glucose levels were measured by placing whole blood (1 μL) on a glucose test strip for immediate analysis (using a plasma blood glucose analyzer [Accu-Chek; Roche Diagnostics, Inc.]). The substrate and insulin values reported in the current article correspond to values obtained at baseline, just before PET. Finally, percentage of glycosated hemoglobin (HbA1C) levels were determined by a 2000 Pet. Finally, percentage of glycosated hemoglobin (HbA1C) levels were determined by a 2000

| TABLE 1 | Animal Demographics, Hemodynamics, and FFA Levels for Lean and ZDF Rats |
|---------|-----------------|-----------------|-----------------|-----------------|-----------------|
|         | Lean W14       | Lean W19       | ZDF W14        | ZDF W19        |
| Weight (g) | 306.37 ± 11.19 | 354.65 ± 23.16 | 316.35 ± 17.66 | 344.08 ± 21.21 |
| HR (bpm)  | 245.50 ± 21.20*| 249.33 ± 31.39*| 207.17 ± 13.29| 198.17 ± 14.61 |
| HbA1C (%) | 3.33 ± 0.12*   | 3.28 ± 0.10*   | 7.72 ± 0.66    | 7.38 ± 0.73    |
| FFA (nmol/mL) | 825.90 ± 300.50* | 1165.32 ± 374.22 | 1728.72 ± 675.59 | 1920.00 ± 890.99 |

*Significantly lower than age-matched ZDF rats.
Values are represented as mean ± 1 SD. P < 0.05 was considered significant. Please refer to “Results” for significance values. HR = heart rate; bpm = beats per minute.

RNA Isolation and Real-Time Reverse Transcription (RT)-Polymerase Chain Reaction (PCR)
After PET image acquisition at week 19 (W19), animals were sacrificed and the heart extracted and frozen at −80°C until RNA was isolated for gene expression analysis. Total RNA was isolated from the heart by using RNAzol B (Tel-Test) according to the manufacturer’s instructions. RNA concentration and purity were determined by spectrophotometric absorbency at 2 dilutions. First-strand cDNA was generated by RT using 500 ng total of RNA and an RT kit (Applied Biosystems). Real-time RT-PCR was performed using a sequence detection system (PRISM 7500 Fast Real-Time PCR Systems; Applied Biosystems) and a reagent (TaqMan Fast Universal Master Mix; Applied Biosystems). Arbitrary units of target gene mRNA were corrected to 36B4 RNA content to control for loading.

Western Blot Analysis
Frozen heart tissues were homogenized in ice-cold buffer containing 50 mM of sodium fluoride, 10 mM of sodium phosphate, 1 mM of ethylenediaminetetraacetic acid, 1 mM of ethylene glycol tetraacetic acid, 1 mM of dithiothreitol, 1% of triton X, and protease inhibitors using a Sonifier (Branson). Samples were incubated on ice for 30 min and then centrifuged for 15 min at 15,000g. The supernatants were collected and the protein concentrations determined. For GLUT-1 and GLUT-4 immunoblots, 5 μg of whole-cell protein were prepared in a nondenaturing sample buffer and subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis. Protein was then transferred from the gel to a nitrocellulose membrane. Membranes were blocked for 1–1.5 h in tris-buffered saline (TBS) containing 0.1% of polyborate 20 (TBS-T) and 5% of nonfat milk. Blots were then probed using antibodies raised in rabbit hosts (anti-GLUT-4 or anti-GLUT-1 [a gift from Mike Mueckler]) overnight at 4°C in TBS-T. Blots were then washed in TBS-T and incubated with donkey antirabbit horseradish peroxidase–labeled IgG secondary antibodies for 1 h at...
room temperature in TBS-T. After a second washing of the blots in TBS-T, bands were visualized by electrochemiluminescence and autoradiographic film.

**Statistical Analysis**

**Differences Between Lean and ZDF Measurements.** A 2-tailed Student t-test was performed to test for significant differences between groups (e.g., lean vs. ZDF). When comparing within a group (i.e., between week 14 [W14] and W19), a paired t-test was performed.

**Dependence of MGUp on Gene Expression of GLUTs.** Regression analysis was performed to characterize the dependence of MGUp on gene expression of GLUT-1 and GLUT-4. Three regression models were used: M1: MGUp = β0 + β1 × [GLUT-1] + β2 × [GLUT-4]; M2: MGUp = β0 + β1 × [GLUT-1]; and M3: MGUp = β0 + β1 × [GLUT-4]. In each model, βi (i = 0 . . . 2) denotes the coefficient of regression and GLUT-1 and GLUT-4 denote gene expression levels of respective GLUTs. Statistical analysis on the significance of βi (i = 0 . . . 2) and the goodness of fit of the models was performed using software (SPSS; SPSS, Inc.). Table 3 summarizes results of the statistical analysis.

In all cases, a P value of less than 0.05 was considered significant.

**RESULTS**

**Hemodynamics and Blood Substrate Levels**

On average, lean rats at W14 and W19 had significantly higher heart rates than age-matched ZDF rats (P = 0.0038, P = 0.0047, respectively). No significant difference in heart rates in the aging rat from W14 to W19 within either the lean or the ZDF group was observed. Compared with lean littermate controls, ZDF rats exhibited significantly increased glucose (P = 0.007), HbA1C (P = 1.84 × 10⁻⁸), FFAs (P = 0.013), and insulin (P = 0.001) levels at W14 (Table 1; Fig. 1). At W19, only HbA1C and glucose remained significantly (P = 8.47 × 10⁻⁸ and P = 0.002, respectively) elevated.

**ECHO Measurements**

ECHO measurements are summarized in Table 2. On average, the diastolic LVID of lean rats at week 13 (W13) was significantly lower than LVIDs of lean rats at week 18 (W18) (P = 0.05) and age-matched ZDF rats (P = 0.013). Similarly, the LV mass (LVM) of lean rats at W13 was significantly lower than at W18 (P = 0.004) and when compared with age-matched ZDF rats at W13 (P = 0.02). We observed no significant differences in fractional shortening (FS) between and within groups.

**PET Measurements**

MGUp and MGU are depicted in Figure 2. ZDF rats exhibited significantly lower glucose uptake rate than did age-matched lean rats at both W14 and W19 (P = 0.006 and 0.0001, respectively). Moreover, the aging lean rat exhibited an increasing uptake rate of glucose from W14 to W19 (P = 0.007), which was not apparent in the aging ZDF rats (Figs. 2A and 2B). MGU in the lean rat was significantly (P = 0.04) higher at W19 than at W14. Finally, MGU in ZDF rats at W19 was significantly (P = 0.04) less than MGU in age-matched lean rats.

**Gene and Protein Expression of GLUT-1 and GLUT-4**

Gene expression levels of mRNA encoding for GLUT-1 and GLUT-4 in the hearts of rats at 19 wk of age are provided in Figure 3A. The expression of GLUT-1 was not altered significantly in ZDF rats, compared with controls. However, gene expression of GLUT-4 was markedly diminished in

<table>
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<th>Table 2: ECHO Measurements for Lean and ZDF Rats</th>
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<td><strong>ECHO measurements</strong></td>
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<tr>
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<tr>
<td>Distolic LV PW (mm)</td>
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<tr>
<td>Systolic LV PW (mm)</td>
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<tr>
<td>LVM (mg)</td>
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<tr>
<td>FS (%)</td>
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<td>Rm-18F</td>
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*Significantly different from age-matched ZDF rats. 
†Significantly different from week 18. Values are represented as mean ± 1 SD. P < 0.05 was considered significant. Please refer to “Results” for significance values. Rm-18F = myocardial recovery coefficient of 18F radionuclide.

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**Table 3: Statistical Analysis of Regression Models Depicting Dependence of MGUp on Gene Expression of GLUT-1 and GLUT-4**

<table>
<thead>
<tr>
<th>Model</th>
<th>β₀</th>
<th>β₁</th>
<th>β₂</th>
<th>F value</th>
<th>P value</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>0.5230</td>
<td>0.7280</td>
<td>0.0020</td>
<td>14.7090</td>
<td>0.0050</td>
<td>0.83</td>
</tr>
<tr>
<td>M2</td>
<td>0.3560</td>
<td>0.3940</td>
<td>0.8260</td>
<td>0.3940</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>M3</td>
<td>0.2970</td>
<td>0.0003</td>
<td>38.2000</td>
<td>0.0003</td>
<td>0.81</td>
<td></td>
</tr>
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ZDF rats ($P = 0.004$). These findings were in agreement with protein expression levels of GLUT-1 and GLUT-4 (Fig. 3B).

**Dependence of MGUp on Gene Expression of GLUTs**

The dependence of MGUp on gene expression of GLUTs is captured in models M1, M2, and M3 (Table 3). When both GLUT-1 and GLUT-4 are considered as covariates (M1), only the inclusion of GLUT-4 is significant ($P = 0.002$), with a correlation coefficient of $r = 0.91$ ($R^2 = 0.83$). When GLUT-1 is excluded from the regression analysis (M3), the inclusion of GLUT-4 is significant at $P = 0.0003$, with a correlation coefficient of $r = 0.90$ ($R^2 = 0.81$), suggesting that GLUT-4 is sufficient to describe the data (Fig. 4).

**DISCUSSION**

Ever since the pioneering work of Sokoloff on $^{18}$F-FDG (32,33), the literature has been ripe with controversy concerning the utility of $^{18}$F-FDG. At the heart of the matter are potential differences in the affinities of $^{18}$F-FDG and glucose for GLUTs and the hexokinase enzyme; the LC has been devised to correct for these differences (33). Most references to LC note a constant value that is applied to $^{18}$F-FDG measures of MGUp. For example, Yokoyama et al. (17) and others (15,31) used an LC equal to 1 in assessing MGU in humans with T2D. Botker et al. (34) proposed that the LC is a function of the rates of transport and phosphorylation of $^{18}$F-FDG and applied the proposed method to assess MGU in humans with ischemic cardiomyopathy (35). Herrero et al. (36) argued that the latter method leads to significant underestimation of glucose utilization in large animals. We chose LC equal to 1 in keeping with previous work on T2D (15,17,31). Nevertheless, further studies are needed to characterize the LC, in particular in small-animal PET imaging of the heart.

The use of $^{18}$F-FDG instead of $^{11}$C-glucose, particularly in small-animal imaging, provides several advantages. As a radiolabeled analog of endogenous glucose, $^{11}$C-glucose is metabolized much like endogenous glucose. Thus, it can be incorporated in the glycogen pool and undergoes anaerobic and oxidative metabolism after phosphorylation and pyruvate formation. Herrero et al. (14) have devised kinetic

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**FIGURE 1.** Peripheral insulin (A) and glucose (B) levels at W14 and W19 in lean and ZDF rats. Significance values are denoted above bar plots. $P$ value of less than 0.05 was considered significant.

**FIGURE 2.** MGUp (A) and MGU (B) at W14 and W19 in lean and ZDF rats. Significance values are denoted above bar plots. $P$ value of less than 0.05 was considered significant.
models to delineate the abovementioned processes in
the human heart. Glucose metabolism in the rodent heart is
significantly faster than that in humans, which may prohibit
the application of complex kinetic models. In contrast, 18F-
FDG is trapped after phosphorylation by hexokinase, thus
providing an enhanced signal. In addition, glucose metabo-
lism generates 11C-lactate, which can further be metabolized,
thus potentially confounding kinetic analysis. Recently,
Herrero et al. have incorporated the contribution of lactate in
a kinetic model of glucose metabolism in the human heart
(13). However, because glucose metabolism is significantly
faster in rodents, it is feasible that the contribution of lactate
to overall PET signal is not trivial in small animals, which
could explain the apparent contradiction between this work
and previous work using 11C-glucose in ZDF rats (25).
Therefore, although further work is needed to correlate 11C-
glucose with 18F-FDG metabolism in small animals, at this
stage 18F-FDG is a unique imaging marker for glucose
metabolism in rodents.

Under normal conditions, glucose metabolism is regulated
through multiple steps including uptake. Glucose uptake,
in turn, is dependent on the transmembrane glucose gradi-
ent and density of GLUT-1 and GLUT-4. GLUT-1 is more
pronounced in the sarcolemma and represents basal glucose
uptake (37). GLUT-4, in contrast, is the dominant transporter
in the adult heart, and under basal conditions a majority of
this transporter is located in the intracellular pool (38). In the
presence of increased insulin levels, GLUT-4 is translocated
to the sarcolemmal membrane (37,38), thus increasing the
density of GLUT-4. In addition, insulin influences glucose
transport through regulation of GLUT gene expression
(39,40). In T2D, insulin resistance results in diminished
translocation of GLUT-4 to the sarcolemmal membrane, thus
affecting glucose transport.

Our data indicates that expression of GLUTs is diminished
in the diabetic heart (Fig. 3). Accordingly, MGUp (Fig. 2A)
is lower in ZDF rats, independent of age. Interestingly,
MGUp was found to be significantly higher in the lean rat at
W19 than that at W14. Although our data do not provide a
full explanation for this observation, the data may suggest
that the heart undergoes a maturation process with glucose
utilization or insulin sensitivity during this time. This is not
observed in ZDF rats, likely because of the progression of
diabetes and associated metabolic changes in this model.
Finally, PET measures of MGUp (Fig. 2) agree with both
protein and gene expression analysis (Fig. 3). Regression
analysis suggests that gene expression of GLUT-4 correlates
significantly with MGUp (Fig. 4). Ideally, the uptake rate
constant, \( K_1 \), should have been correlated with gene expres-
sion levels; however, because of limitations in the temporal
sampling and noisy nature of initial frames, we were unable
to characterize \( K_1 \). Nevertheless, \( K_1 \) is a scaling factor in
calculating MGUp. Taken together, our findings support
the notion that PET measures of MGUp correlate with the
density of GLUT-4 and its regulation by insulin.

While it is interesting to note that MGUp is significantly
higher in lean rats than it is in age-matched ZDF rats at W14,
no statistical difference in total MGU (Fig. 2B) is exhibited.
The main difference between the 2 measures is that the for-
ermer captures the intrinsic capacity of the heart to use glucose
while the latter includes peripheral effects, namely peri-
pheral concentration of glucose. Hyperglycemia in the ZDF rat
at W14 countered reduced MGUp. At W19, however, MGUp

![FIGURE 3. (A) GLUT-1 and GLUT-4 gene expression levels in
lean and ZDF rats at W19. Gene expression was normalized to
levels observed in lean rats. Significance values are denoted
above bar plots. \( P \) value of less than 0.05 was considered
significant. (B) Representative autoradiographic results of
Western blot analyses performed with antibodies for GLUT-1
and GLUT-4 on whole-cell lysates of hearts of lean and ZDF rats
at W19. AU = arbitrary units.]

![FIGURE 4. Regression model M3 was used to characterize
dependence of MGUp on gene expression of GLUT-4 with \( R^2 =
0.81 \), which is significant at \( P = 0.0003 \).]
in the lean rat is significantly higher than it is at W14. Alterations in total glucose utilization are apparent by W19 and possibly earlier. We did not observe diminished FS (Table 2), a measure of contractile dysfunction, in the time course of the study. Zhou et al. (12), however, report diminished contractile function in the 20-wk-old ZDF rat. Thus, PET measures of MGUp and MGU may provide complementary measures of disease, with MGUp capturing early alterations in cardiac-intrinsic mechanisms preceding contractile dysfunction.

CONCLUSION

Noninvasive imaging of myocardial metabolism can provide invaluable information about the metabolic state of the heart. Small-animal PET, in particular, offers a unique platform to validate new imaging probes and targets as well as novel therapeutic interventions for translation to humans. In this article, we used small-animal PET with 18F-FDG to quantify myocardial glucose metabolism in an animal model of T2D, namely the ZDF rat. We characterized, noninvasively, alterations in myocardial glucose metabolism, consistent with theories about the etiology of diabetic cardiomyopathy. In particular, we demonstrated reduced MGUp, independent of age, in the ZDF diabetic heart. Differences in MGU were apparent only at late stages of diabetes, suggesting that alterations in MGUp may provide an early imaging marker for diabetic cardiomyopathy. Finally, we validated 18F-FDG PET measures of MGUp rate against gene and protein expression of GLUTs. Our findings underscore both the translational capability and the potential use of small-animal PET in assessing the efficacy of therapies.

ACKNOWLEDGMENTS

We thank Lori Strong, Margaret M. Morris, Amanda Roth, Paul Eisenbeis, Ann Stroncek, and Jerrel Rutlin for technical assistance and the Washington University School of Medicine cyclotron staff for synthesis of radiopharmaceuticals. This work was supported by NIH/NHLBI grant 2-PO1-HL-13851.

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Published online: July 16, 2008.
Doi: 10.2967/jnumed.108.051672

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