Noninvasive Measurement of Mouse Myocardial Glucose Uptake with ^{18}F-FDG

TO THE EDITOR: I read with interest the recent publication by Thorn et al. (*1*) using vena cava image-derived input functions for quantification of myocardial glucose uptake (MGU). The authors demonstrated that using vena cava PET image–derived input functions permits reproducible noninvasive measurement of regional MGU using ^{18}F-FDG and Patlak kinetic modeling and shows the expected reduction of MGU in type 1 diabetic mice. However, for accurate quantification of MGU, it is critical that plasma glucose time–activity curves be used rather than whole-blood time–activity curves. As discussed previously in this journal (*2,3*), whereas glucose equilibrates extremely rapidly across the erythrocyte plasma membrane in primates, this is not true in adult nonprimates (*4,5*). Transport of glucose into human erythrocytes was too fast to measure at 37°C, whereas in rat erythrocytes transport was more than 3 orders of magnitude slower, even when compared with human erythrocytes at 4°C (*5*). Slower glucose transport rates result in lower erythrocyte-to-plasma glucose distribution ratios in nonhuman primates; ratios ranged from 0 in pigs to 0.45 in calves (*4*). More recently, Wu et al. confirmed that ^{18}F-FDG transport was also slow in mice; the ^{18}F-FDG concentration in plasma was initially significantly higher than in whole blood and did not reach steady state until approximately 20 min after injection (*6*). There was little animal-to-animal variability; estimation of plasma ^{18}F-FDG from whole blood values was possible using an empirically derived exponential function, but this would need validation for different experimental conditions such as diabetes (*6*).

The slow transport of ^{18}F-FDG across the erythrocyte plasma membrane also has implications for the lumped constant (LC) of 0.67 used by Thorn et al. to account for differences in uptake and phosphorylation of ^{18}F-FDG versus glucose. As discussed previously (*2,3,7*), the study by Ratib that established the widely used value of 0.67 for the LC calculated MGU as the product of plasma glucose and myocardial blood flow, assuming equal plasma and whole-blood glucose concentrations and rapid equilibration of glucose across the erythrocyte (*8*). However, whereas this would be valid in primates, in dogs the erythrocyte glucose concentration is much lower than the plasma glucose concentration, 1.5 mM versus 4.4 mM (*9*), and the erythrocyte glucose transport rate much slower than cardiac glucose uptake, and so cardiac glucose utilization is essentially derived exclusively from the plasma compartment. MGU can therefore be estimated as the product of plasma flow and the arteriovenous plasma glucose concentration difference (*7*). Using whole-blood flow to calculate MGU will result in artificially high values, resulting in underestimation of the LC. Kofoed et al. found an LC of 1.1 in healthy dogs using plasma flow to calculate MGU (*7*). Estimates of the LC obtained in human volunteers ranged from 1 during insulin infusion to 1.4 in the fasted state (*10*).

In summary, for nonprimates slow transport of glucose across the erythrocyte membrane makes it critical to use plasma rather than whole-blood ^{18}F-FDG time–activity curves when determining MGU rates with ^{18}F-FDG and PET. The value of 0.67 for the LC used to account for differences in the uptake and phosphorylation of ^{18}F-FDG versus glucose is an underestimate, which will result in overestimation of MGU.

DISCLAIMER

The views expressed are those of the author and do not necessarily reflect those of the National Heart, Lung, and Blood Institute.

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Published online Mar. 20, 2014.
DOI: 10.2967/jnumed.113.135152

REPLY: We wish to thank Dr. Buxton for his letter to the editor, describing the effects of red blood cell uptake (plasma–to–whole-blood activity ratio) and transport/phosphorylation of ^{18}F-FDG versus glucose (lumped constant [LC]) for accurate quantification of the rate of myocardial glucose uptake (rMGU) in mice. Our study (*1*) showed that the image-derived blood input function (IDIF) within a region of interest in the mouse vena cava can be used for repeatable assessment of the blood time–activity curve for Patlak kinetic modeling of rMGU in healthy control Friend virus B–type mice. We also demonstrated the utility of this

methodology to detect serial changes of rMGU in streptozotocin-induced type 1 diabetic mice at baseline, after diabetes induction, and after acute insulin treatment. The small size of the mouse LV cavity, on the order of the spatial resolution of the current small-animal PET imaging systems, results in substantial myocardial activity spillover into the mouse left ventricular cavity region and inaccurate assessment of the blood IDIF.

In this paper we assumed an LC of 0.67 for estimation of myocardial glucose uptake, according to previous ^{18}F-FDG measurements in mongrel dog hearts (*2*). The reported LC values in mouse ^{18}F-FDG studies range from 0.6 to 1.0 (*3,4*). We agree that more research is needed to verify the accuracy of LC values for mouse ^{18}F-FDG studies in relation to blood glucose levels and organ blood flow, potentially using methods such as those proposed by Wiggers et al. (*5*). These studies will need to control for multiple variables such as fed versus fasted versus glucose-clamp state, disease model or phenotype, background strain of the mouse, and anesthetic protocol, all of which can affect the LC value. The particular assumed LC value in our study determines the absolute scale of the rMGU values but does not change the relative (%) values of test–retest repeatability or population variability as reported.

It is true that the LC may be reduced in the type 1 diabetic model compared with both baseline and acute insulin treatment. As reported in Schuier et al. (*6*), the LC for the brain in rats decreased very gradually with increasing plasma glucose concentration, from 0.45 at normoglycemic range (7–8 mM) to 0.38 at hyperglycemic range (28–31 mM). If the same effect was assumed to occur in the mouse heart, this would reduce the reported difference in rMGU between baseline and type 1 diabetes by about 15% (although there are no data to confirm or refute this assumption). Because the reported diabetic rMGU was reduced by 60% versus baseline, the observed reduction would still be significant, demonstrating the utility of the vena cava IDIF for precise serial estimation of the rMGU in this mouse model of diabetic disease and therapy, using each animal as its own control.

Although the plasma time–activity curve may be more accurate to determine the absolute rMGU values, the primary goal of the present study was to confirm the validity of the sampled arterial whole blood versus the IDIF. It is not possible to directly measure plasma concentrations from the whole-blood regions of interest on the PET image; therefore, we agree that plasma–to–whole-blood corrections should ideally be performed. Similar to the LC effects described above, additional studies may be required to fully characterize the effects of variable red blood cell uptake on rMGU values in mice. Assuming these effects are small between experimental conditions using the same species, strain, diet, anesthetic, and other variables, we are proposing methodology that is similar to what has been used in clinical studies, allowing for the potential translation of serial rMGU PET imaging from mouse models to application in evaluation of disease phenotype and therapy in human patients.

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Published online Mar. 20, 2014.
DOI: 10.2967/jnumed.114.138214