VIII. 7. \([^{18}\text{F}]\text{FDG-PET Measurement of Glucose Metabolism during Exercise Using Two Analytical Approaches}

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\text{Background}

Our previous reports\(^1,2\) employed the semiquantification method (standardized uptake values: SUV) to assess organ glucose metabolism after exercise with \(^{18}\text{F}\)-2-fluoro-2-deoxyglucose and three-dimensional positron emission tomography technique ([\(^{18}\text{F}\)]\text{FDG and 3D-PET}). Recently, Kemppainen J. and co-workers assessed glucose metabolism of lower limb muscles and myocardium using absolute quantification method (rMRGlc)\(^3\). However, no reports have evaluated glucose metabolic changes at whole-body level after exercise task with 3D-PET technique, comparing semiquantitative and quantitative analytical methods. We tried to elucidate the workloads-induced organ glucose metabolism using two analytical methods (semiquantitative and quantitative), as to establish relationship between two PET quantification approaches.

\text{Methods}

Eleven healthy male volunteers collaborated with this investigation. All subjects abstained from eating and drinking for at least 5 hours before the experiment. They were asked not to perform any kind of physical exercise from one day before investigation. 5 subjects served as exercise group whose ages ranged from 21 to 23 y (21.80 ± 0.84 y; mean ±S.D.). Another 6 subjects, aged mean 24 ± 5.34 y (range; 19 ~ 33 y) were studied as resting control maintaining the same study protocol without exercise. \([^{18}\text{F}]\text{FDG dose for control was in average 42.48 ± 6.63 MBq (mean ± S.D.}.\) A written fully informed consent was obtained from each subject before the study. This study protocol was approved by the Clinical Committee for Radioisotope Studies of Tohoku University.
Ergometer bicycle exercise was arranged at 40% and 70% $\dot{V}O_2\text{max}$ workloads. $\dot{V}O_2\text{max}$ was measured by intermittent exercise on an ergometer bicycle (Monark 818E, Sweden), and oxygen consumption rate was determined by an automated metabolic unit machine (AE280-S, Minato Co. Ltd. Osaka, Japan). Before the experiment, subjects rested for 20 minutes in a dim lit quiet room. One teflon catheter was inserted to their antecubital veins of the left hand for blood sampling to measure plasma glucose, lactate and insulin. Another teflon catheter was inserted to opposite antecubital veins for $[^{18}\text{F}]$FDG administration. Then, they started ergometer bicycle riding at the speed of 60 revolution/min (Monark 818E, Sweden) at both workloads (40% and 70% $\dot{V}O_2\text{max}$). $[^{18}\text{F}]$FDG was injected through a catheter at 10 min later following exercise task. The radioactivity dose for the exercise group was 38.37 ± 2.15 MBq (mean ± S.D.). After injection, subjects continued to pedal the bicycle for another 30 min, completing a total of 40 min task. Immediately after intravenous administration of $[^{18}\text{F}]$FDG, heated arterialized venous blood was sampled from cubital vein opposite to the injection site. Plasma $[^{18}\text{F}]$FDG concentrations were measured both during exercise and PET scan for 24 times. Plasma metabolite concentrations (i.e., Glucose, lactate and insulin) were measured at two points such as pre and post exercise states.

Subjects lay down in supine position on PET table with eyes open following exercise task. The PET room was kept dimmed and quiet. The scan protocol was as follows: a 3 dimensional (3D) whole-body emission scan (3 min × 9F) was performed from knee to the vertex followed by transmission scan (3 min × 9F) using a PET apparatus (SET2400W, Shimadzu, Kyoto, Japan). The transmission scan (post-injection mode) was performed with a $^{68}\text{Ge}/^{68}\text{Ga}$ external rotating line source (370 MBq at purchase).

Regions of interest (ROIs) were set on the skeletal muscles of thigh, lumbar/gluteal regions, and visceral organs such as liver, heart and brain etc. (Figure 1). To evaluate the rate of glucose utilization, an autoradiographic method was applied using the following equation:

$$rMRGlc = \frac{Cp}{LC} \left[ \frac{K_1^* k_{\text{m1}}}{K_1^* k_{\text{m2}} + k_{\text{m3}}^*} \right] \frac{C^* i(T) - C^* e(T)}{C^* m(T)}$$

In another, semiquantitative analysis (Standard uptake value; SUV) was done by using the following equation:

$$\frac{Mean \ ROI \cts (cps/pxls) \times Body \ weight (g)}{Injected \ dose (\muCi) \times Calibration \ factor (cps/\muCi)}$$
Group comparisons were done by using one-way analysis of variance (ANOVA) and Tukey’s test (post-hoc) analysis. The significant differences were set at p<0.05. Correlation was calculated using Pearson’s correlation coefficient analysis.

Results

[¹⁸F]FDG uptake was only remarkable in the brain, heart and urinary bladder in the resting subject, while high uptake was visualized in skeletal muscles at exercise state (Fig. 1). Glucose metabolism (SUV and rMRGlc) was increased in the skeletal muscles of thigh and lumbar/gluteal regions (p<0.05), and was decreased in the brain (p<0.05) after exercise task (40% and 70% VO₂max workloads). A correlation between SUV and rMRGlc was found among organs (i.e., Thigh, liver, heart and brain), except in the lumbar/gluteal muscles. Figure 2 clearly depicted a good correlation between SUV and rMRGlc in the brain (a) and heart (b); however, a non-suggestive correlation was found in the lumbar/gluteal skeletal muscle (c). The changes in plasma metabolites were as follows: stable plasma glucose concentrations, an increase (p<0.05) plasma lactate concentration at post-exercise condition of 70% VO₂max (5.3 ± 2.4 mmol/liter) to compare with pre-exercise condition (0.9 ± 0.2 mmol/liter). The plasma insulin concentration was decreased (p<0.05) only at post-exercise workload of 70% VO₂max (2.0±0.7 μU/mol) than pre-exercise condition (4.6±1.5 μU/mol).

Conclusion

Organ glucose uptake either increased or decreased almost linearly with exercise loads up to moderate workload (70% VO₂max). In spite of complexity of energy metabolic controls such as glucose-fatty acid metabolic interaction, aerobic-anaerobic interaction, and involvement of glycogenolysis ⁵), exercise-induced organ glucose metabolism were successfully assessed with [¹⁸F]FDG-3D-PET technique and two analytical approaches. Organ glucose uptake either increased or decreased almost linearly with exercise loads up to moderate workload (70% VO₂max), suggesting of homeostatic metabolic control. Semiquantitative method without blood samplings was found useful to estimate a rough trend of glucose consumptions. However, one organ failed to have good correlations between SUV and rMRGlc, the lumbar and gluteal muscles for example, which demonstrates that semiquantitative approach needs a great care when metabolic rate of glucose utilization changes at whole-body level.
References


Figure 1. ROIs procedure and [18F]FDG uptake of individual organs at rest (left) and exercise loads; 40% and 70% VO2max (right).

Figure 2. Correlation between SUV and rMRGluc in the viscera (a, b) and skeletal muscle (c), showing good correlation in the brain (a) and heart (b), and non-suggestive correlation in the lumbar/gluteal muscle (c).