Effect of postprandial hyperglycaemia in non-invasive measurement of cerebral metabolic rate of glucose in non-diabetic subjects

Tatsuro Tsuchida[1], Norihiro Sadato[2], Sadahiko Nishizawa[2], Yoshiharu Yonekura[2], Harumi Itoh[1]

[1] Department of Radiology, Fukui Medical University, 23 Shimoaizuki, Matsuoka, Fukui, 910–1193, Japan
[2] Biomedical Imaging Research Center, Fukui Medical University, Fukui, Japan

Received 18 August and in revised form 14 October 2001 / Published online: 29 November 2001

Abstract. The aim of this study was to determine the effect of postprandial hyperglycaemia (HG) on the non-invasive measurement of cerebral metabolic rate of glucose (CMRGlc). Five patients who had a meal within an hour before a fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) examination were recruited in this study. They underwent intermittent arterial blood sampling (measured input function), and, based on this sampling, CMRGlc was calculated using an autoradiographic method ($CMRGlc_{real}$). Simulated input functions were generated based on standardised input function, body surface area and net injected dose of FDG, and simulated CMRGlc ($CMRGlc_{sim}$) was also calculated. Percent error of the area under the curve (AUC) between measured (AUC_{real}) and simulated input function (AUC_{IFsim}) and percent error between $CMRGlc_{real}$ and $CMRGlc_{sim}$ were calculated. These values were compared with those obtained from a previous study conducted under fasting conditions (F). The serum glucose level in the HG group was significantly higher than that in the F group (165±69 vs 100±9 mg/dl, P=0.0007). Percent errors of AUC and CMRGlc in grey matter and white matter in HG were significantly higher than those in F (12.9%±1.3% vs 3.5%±2.2% in AUC, P=0.0015; 18.2%±2.2% vs 2.9%±1.9% in CMRGlc in grey matter, P=0.0028; 24.0%±4.6% vs 3.4%±2.2% in CMRGlc in white matter, P=0.0028). It is concluded that a non-invasive method of measuring CMRGlc should be applied only in non-diabetic subjects under fasting conditions.

Keywords: FDG-PET – CMRGlc – Standardised input function – Hyperglycaemia

Tatsuro Tsuchida (✉)
Department of Radiology, Fukui Medical University,
23 Shimoaizuki, Matsuoka, Fukui, 910–1193, Japan
e-mail: tsucchy@fmsrsa.fukui-med.ac.jp
Tel.: +81-776-613111 ext 2335

Eur J Nucl Med (2002) 29:248–250
DOI 10.1007/s00259-001-0701-5

Introduction

We previously reported a method of measuring the cerebral metabolic rate of glucose (CMRGlc) non-invasively via a standardised input function [1] and an autoradiographic method. In that study, all subjects underwent a fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) examination under fasting conditions. Non-invasive measurement of CMRGlc, which requires two-point arterialised venous sampling, has also been performed by Eberl et al. [2] in both fasting normal subjects and hyperglycaemic patients with diabetes mellitus (DM). In their study, errors of input function in the patients with diabetes mellitus were not significant compared with those in normal subjects. They speculated [2] that a greater amount of error may be introduced if patients are not fasting or if they are studied immediately after a meal. In these situations, possible changes in blood glucose levels during the uptake and study period might cause additional errors due to violation of the steady state assumption of the model. However, no one has reported on the errors in CMRGlc in non-diabetic subjects under fasting and hyperglycaemic conditions. Hence, we aimed to determine whether a non-invasive method is applicable for patients in a hyperglycaemic state.

Materials and methods

The theory underlying the method used in this study has been described in detail in our previous paper [1]. Five patients (one man and four women) who had eaten a meal within an hour before the FDG-PET examination were recruited for this study as the postprandial hyperglycaemic group (HG). Another group of ten pa-

tients (four men and six women) who had undergone brain FDG-PET studies while fasting for at least 6 h were also included as the fasting group (F). All patients were non-diabetic, which was confirmed by measuring their serum glucose level and HbA1c.

For this examination, the patient's head was immobilised with a head-holder. Small plastic catheters were placed in the radial artery of one arm for arterial sampling and in the antecubital vein of the other arm for the radiotracer injection. The protocol followed in this study was approved by the ethical committee of Fukui Medical University, and all subjects gave their written informed consent for the study.

PET scanning was performed with a GE Advance system (GE, Milwaukee, Wis., USA). After a 10-min transmission scan, FDG in a dose of 293–490 MBq (mean±SD, 377±60 MBq) was administered via the cubital vein for more than 30 s. Dynamic scans were obtained up to 60 min after the injection, via arterial sampling. In this study, data from measurements taken 50–60 min post injection were used for the calculation of CMRGlc via an autoradiographic method [3]. Plasma glucose concentrations were measured in all patients immediately after the last scan. After the first FDG injection, 2 ml of arterial blood was sampled every 15 s in the first 2 min and then at 3, 5, 7,10, 15, 20, 30, 45 and 60 min after the injection. The sampled blood was centrifuged, and 0.5 ml of plasma was collected from each tube. The plasma radioactivity was measured by a scintillation counter, against which the PET camera was cross-calibrated using a cylindrical phantom filled with the ^{18}F solution.

Standardised input function with body surface area correction (SIF), which had been generated in the previous study, was applied in order to calculate the simulated input function (IFsim). For the estimation of IFsim, the area under the curve (AUC), which indicates the time integral of the plasma input function from 0 to 60 min, was used. The percent error of estimation of AUC was calculated by means of the following equation:

$$\%\ \text{error of estimation of AUC} = \left| \frac{AUC_{IFsim} - AUC_{real}}{AUC_{real}} \right|$$

where AUC_{real} is the area under the curve obtained from the measured input function, and AUC_{IFsim} is the area under the curve obtained from the IFsim.

For the estimation of CMRGlc, % error of estimation of CMRGlc was used, which was obtained from the following equation:

$$\%\ \text{error of estimation of CMRGlc} = \left| \frac{CMRGlc_{sim} - CMRGlc_{real}}{CMRGlc_{real}} \right|$$

here $CMRGlc_{real}$ is calculated with the measured input function, and $CMRGlc_{sim}$ is calculated with the IFsim. Percent error of estimation of CMRGlc was obtained for every value of $CMRGlc_{real}$ in all patients. This procedure has been described in detail in our previous paper [1]. In particular, the percent error of estimation in grey and white matter was obtained for the $CMRGlc_{real}$ values of 7.3 and 3.4 mg/min/100 g, respectively, which are reported to be the mean normal values [4].

Statistical analysis. The *t* test was used for the comparison of plasma glucose levels of patients and the difference in % error between F and HG groups. Statistical significance was defined as $P<0.05$.

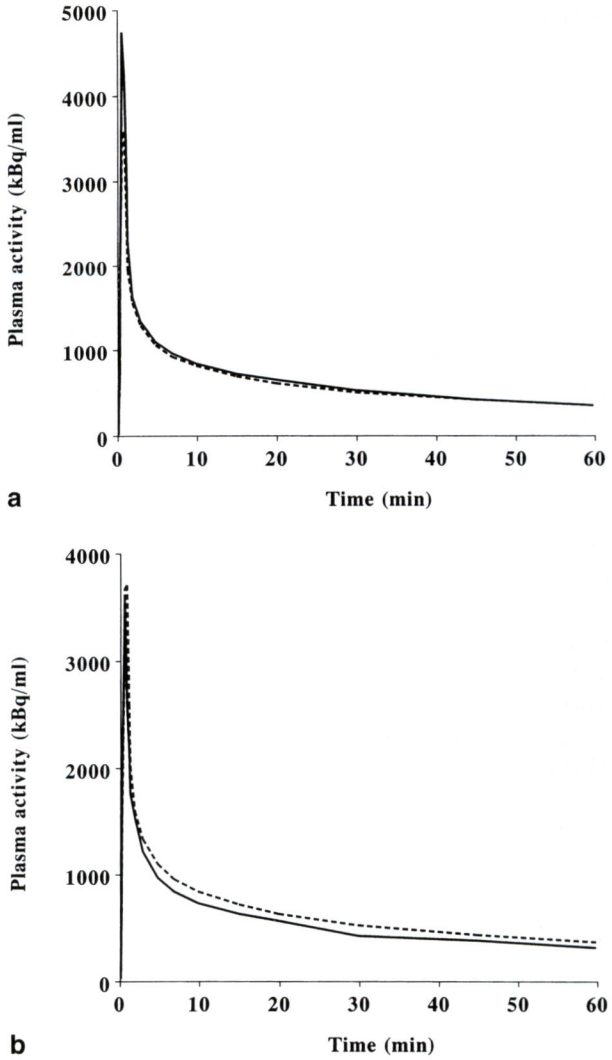

Fig. 1a, b. Example of measured and simulated input function in F (**a**) and HG (**b**). *Solid line* represents the measured input function; *dotted line* represents the simulated input function

Results

The serum glucose level in the HG group was significantly higher than that in the F group (165±69 vs 100±9 mg/dl, $P=0.0007$).

Figure 1 shows the typical measured and simulated input function in the F and HG groups. In the F group, the measured and simulated input function were almost identical (Fig. 1a). On the other hand, an overestimation of the simulated input function was observed in the HG group (Fig. 1b). Percent errors of AUC and CMRGlc in grey matter and white matter in the HG group were significantly higher than those in the F group (12.9%±1.3% vs 3.5%±2.2% in AUC, $P=0.0015$; 18.2%±2.2% vs 2.9%±1.9% in CMRGlc in grey matter, $P=0.0028$; 24.0%±4.6% vs 3.4%±2.2% in CMRGlc in white matter, $P=0.0028$).

Discussion

This study revealed that, as speculated by Eberl et al. [2], non-invasive measurements of CMRGlc are less reliable under a postprandial hyperglycaemic condition than under a fasting condition. As shown in Fig. 1b, the simulated input function was overestimated compared with the measured input function in the HG group. In brain FDG studies, an insulin clamp procedure showed accelerated plasma clearance of FDG [4], which was attributed mainly to increased tissue uptake of FDG due to induction of the glucose transporter. Although we did not measure the insulin level in each patient in the present study, an increase in insulin levels must have occurred, inducing the translocation of glucose transporters from an intracellular component to the plasma membrane, because all subjects were non-diabetic. The clearance rate of FDG from plasma may have been slower than that in HG because SIF, which was used to calculate IFsim, was generated from arterial sampling data during F. This would have caused the overestimation in the HG group, and led to a large % error of AUC and CMRGlc (since CMRGlc is dependent on the AUC of the input function to the time of scanning) [5]. In the calculation of CMRGlc a fasting state is recommended in order to maintain a steady state of glucose concentration, and the precision of CMRGlc in the hyperglycaemic state is consequently not assured. Eberl et al. only speculated that a larger error in input function occurs during the fluctuation of the blood glucose level. Hence, in this study we attempted to reveal the effect of postprandial hyperglycaemia on the measurement of CMRGlc.

In conclusion, in the application of a non-invasive method, the change in input function due to hyperglycaemia causes a larger error in the measurement of AUC and subsequently in that of CMRGlc. Therefore, subjects need to be kept in a fasting state when a non-invasive method is applied.

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