Noninvasive Measurement of Cerebral Metabolic Rate of Glucose Using Standardized Input Function

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The purpose of this study was to propose and validate a method for the noninvasive measurement of cerebral metabolic rate of glucose (CMRGlc) by fluorodeoxyglucose (FDG) PET with a standardized input function (SIF) and an autoradiographic method. **Methods:** Plasma input functions, measured by intermittent arterial blood samplings after the intravenous injection of FDG, in 44 patients who had fasted for at least 6 h, were used to generate the SIF. The input function of each patient was normalized with the net injected dose (nID) of FDG and body mass as indicated by body surface area (BSA) or body weight (BW). The SIF was generated as an average of 44 normalized input functions. The estimation of the input function and CMRGlc with SIF was validated in 10 additional patients, who underwent FDG PET after fasting for at least 6 h. CMRGlc was estimated with a simulated input function (IFsim) generated with the following equation: IFsim = SIF × (nID/body mass). The estimated CMRGlc was compared with the measured CMRGlc. **Results:** Based on BSA, the percentage error of the area under the curve of IFsim was 3.5% ± 2.2%. The percentage error of CMRGlc was 2.9% ± 1.9% in gray matter and 3.4% ± 2.2% in white matter. A similar percentage error was obtained based on BW. **Conclusion:** The proposed method is noninvasive and accurate, and therefore is clinically acceptable for measuring CMRGlc in patients in fasting states.

Key Words: FDG PET; cerebral metabolic rate of glucose; standardized input function

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The autoradiographic method with ^{18}F-fluorodeoxyglucose (FDG) and PET for measurement of the regional cerebral metabolic rate of glucose (CMRGlc) has been well established. This model, originally developed by Sokoloff et al. (*1*) in the albino rat, has been validated in humans with dynamic and static scans (*2–4*). This method requires the measurement of arterial plasma FDG concentration as an input function, and, hence, multiple arterial blood samplings are necessary. Because frequent arterial blood samplings may not be feasible in clinical settings, several attempts have been made to simplify the procedure. The arteriovenous method, using a heated limb (*2,5*) eliminates the discomfort of arterial puncture, but the prolonged warming to ensure adequate arteriovenous shunting may not be comfortable, and there is still the need for frequent blood sampling. Techniques to estimate the input function from a population-based standard arterial input curve for FDG have been attempted with calibration using two-point arterial blood samplings (*6*) or two-point arteriovenous samplings (*7*).

We now propose a method for the noninvasive measurement of CMRGlc that uses a population-based standardized input function (SIF) and does not require blood sampling. The method is based on the assumption that the shape of the input function is the same across subjects. The purpose of this study was to generate a population-based SIF calibrated with net injected dose (nID) of FDG and body mass ([BM], body surface area [BSA] or body weight [BW]), to estimate CMRGlc with SIF using an autoradiographic technique (*2*) and to validate the estimation by comparing the estimated CMRGlc with the measured CMRGlc.

MATERIALS AND METHODS

Theory

Takikawa et al. (*6*) attempted to estimate the individual plasma input function using a population-based input function based on the assumption that the shape of the input function across subjects is the same. Considering that the area under the curve (AUC) of the input function is the most direct comparison of the input function and can be used to scale the input function (*6*), they tried to estimate the AUC by arterial sampling 10 min and 45 min after the injection of FDG. Our method is an extension of their idea, in that the scaling factor can be estimated without arterial sampling.

If the input function of subject i is expressed as the sum of multiple exponential functions:

$$C_i(t) = \sum_j C_{ij}(0)\exp(-k_{ij}t), \qquad \text{Eq. 1}$$

where j^{th} exponential function has height of $C_{ij}(0)$ and decay

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constant of k_{ij}, the AUC of subject i (AUC_i) from t = 0 to T is:

$$AUC_i = \int_0^T C_i(t)dt = \int_0^T \sum_j C_{ij}(0) \exp(-k_{ij}t)dt$$

$$= \sum_j \frac{C_{ij}(0)}{k_{ij}}(1 - \exp(-k_{ij}T)), \quad \text{Eq. 2}$$

for T:

$$AUC_i = \sum_j \frac{C_{ij}(0)}{k_{ij}}, \quad \text{Eq. 3}$$

with the assumption that the shape of the input function is the same across subjects, k_{ij} and the ratio of $C_{ij}(0)$ are the same across patients. $C_i(0)$ is the initial plasma concentration of FDG of patient i with an assumption of instant mixing of FDG in the initial distribution volume at t = 0 (*8*), and r_j is the ratio of $C_{ij}(0)$ to $C_i(0)$, $k_{ij} = k_j$, $r_{ij} = r_j$.

$$AUC_i = \sum_j \frac{C_i(0)r_j}{k_j} = C_i(0) \sum_j \frac{r_j}{k_j}. \quad \text{Eq. 4}$$

From Equation 4, $C_i(0)$ is proportional to AUC_i; therefore, $C_i(0)$ can be used to scale the input function:

$$\frac{C_i(t)}{C_i(0)} = \frac{1}{C_i(0)} \sum_j C_{ij}(0)\exp(-k_{ij}t) = \sum_j r_j \exp(-k_{ij}t)$$

$$= \sum_j r_j \exp(-k_j t). \quad \text{Eq. 5}$$

Because the right side of Equation 5 is independent of i, $C_i(t)$ is normalized with $C_i(0)$.

By definition, $C_i(0)$ is obtained by dividing the injected dose (ID) by the initial distribution volume of FDG. Because the initial distribution volume of FDG is proportional to BM (*8,9*):

$$C_i(0) = \frac{R_i ID_i}{BM_i}, \quad \text{Eq. 6}$$

where R_i is the ratio of BM to the initial distribution volume of patient i.

Combining Equations 5 and 6:

$$\frac{C_i(t)}{\left(\frac{ID_i}{BM_i}\right)} = R_i \sum_j r_j \exp(-k_j t). \quad \text{Eq. 7}$$

Note that normalization of the plasma input function with ID and BM is influenced by the variation of R_i among subjects. The SIF for a population of number n can be obtained by averaging:

$$SIF(t) = \frac{\sum_{i=1}^{n} ((BM_i/ID_i)C_i(t))}{n}. \quad \text{Eq. 8}$$

Conversely, individual plasma input function can be estimated once data on SIF, ID and BM are available:

$$C_i(t) = \left(\frac{ID}{BM_i}\right) SIF(t). \quad \text{Eq. 9}$$

Our approach to the validation of this noninvasive measurement of CMRGlc is: (a) the production of a population-based SIF in one group by averaging input functions normalized by ID and BM; (b) the calculation of CMRGlc in another group using individual plasma input functions estimated by ID, BM and SIF; and (c) validation of the estimated CMRGlc by comparison with CMRGlc calculated with the measured input function.

Patients

Forty-four patients (20 men, 24 women) who underwent brain FDG PET studies after fasting for at least 6 h were included in the analysis of arterial input data (group 1). Their mean age was 56.4 ± 13.9 y; height, 158.7 ± 7.8 cm; weight, 52.9 ± 9.6 kg; and BM index (BMI), 20.9 ± 2.7 kg/m^2. BMI, a measure of body habitus, was calculated from the equation BMI = body weight (kg)/(height (m))^2. Diagnoses included brain tumor (n = 20), spinocerebellar degeneration (n = 12) and cerebrovascular disease (n = 12). All patients were nondiabetic, with mean plasma glucose levels of 93 ± 13 mg/dL.

Another group of 10 patients (4 men, 6 women) were included in the validation of the estimated CMRGlc calculated with the SIF (group 2). Their mean age was 63.5 ± 13.2 y; height, 158.2 ± 6.8 cm; weight, 57.6 ± 6.6 kg; and BMI, 22.6 ± 2.5 kg/m^2. This group included 4 patients with brain tumors and 6 patients with cerebrovascular disease. These patients, who underwent PET studies after fasting for at least 6 h, were also nondiabetic, with mean plasma glucose levels of 100 ± 9 mg/dL.

Each patient's head was immobilized with head holders. 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 was approved by the ethical committee of Fukui Medical University (Fukui, Japan), and all subjects gave their written informed consent for the study.

PET Procedure

FDG was produced by the method of Hamacher et al. (*10*), with an automated FDG synthesis system (NKK, Tokyo, Japan) and a small cyclotron (OSCAR3; Oxford Instruments, Oxford, UK). PET scanning was performed with a GE Advance system (General Electric, Milwaukee, WI). The performance characteristics of this scanner have been described in detail by DeGrado et al. (*11*). This system permits the simultaneous acquisition of 35 transverse slices with interslice spacing of 4.25 mm with septa (two-dimensional mode). Images were reconstructed to a full width at half maximum of 4.2 mm in both the transaxial and axial directions. The field of view and pixel size of the reconstructed images were 256 mm and 2 mm, respectively. Transmission scans were obtained for 10 min using a standard pin source of $^{68}Ge/^{68}Ga$ for attenuation correction of the emission images. FDG (293–490 MBq, mean ± SD 377 ± 60 MBq), diluted to 10 mL with saline, was administered through the cubital vein over 30 s. Dynamic scans were obtained up to 60 min after the injection, with arterial sampling. The mode of dynamic data acquisition consisted of four 30-s frames, eight 60-s frames and five 600-s frames. In this study, data from only one 600-s frame at 50–60 min were used for the calculation of CMRGlc with an autoradiographic method (*2*). Plasma glucose concentrations were measured in all patients immediately after the last scan. From the time of 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 injection. The dose of FDG in the syringe was measured before and after injection to obtain the nID. 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.

Standardized Input Function with Body Surface Area Correction

The plasma input function of each patient in group 1 was normalized with nID and BSA, and the SIF with BSA correction (SIFbsa) was calculated with Equation 8. BSA was obtained from the following formula (*12*):

$$BSA(m^2) = h^{0.444} \times w^{0.663} \times 88.83 \times 10^{-4}, \quad \text{Eq. 10}$$

where h is height (cm) and w is weight (kg).

Estimation of Input Function

AUC, which indicates the time integral of the plasma input function from 0 to 60 min, was used for the estimation of input function. The percentage error of estimation of AUC was calculated with the following equation:

% error of estimation of AUC =

$$\left|\frac{AUC_{IFsimbsa} - AUC_{real}}{AUC_{real}}\right| \times 100, \quad \text{Eq. 11}$$

where AUC_{real} is the AUC obtained from the measured input function and $AUC_{IFsimbsa}$ is the AUC obtained from the SIFbsa. The percentage error of estimation was calculated in group 2.

Calculation of Cerebral Metabolic Rate of Glucose

For the calculation of CMRGlc in group 2, an autoradiographic method was applied given the following equations (*2,5*):

$$CMRGlc = \frac{Cp}{LC} \times \frac{\left[Ci(T) - \frac{k_1}{\alpha_2 - \alpha_1}\{(k_4 - \alpha_1)e^{-\alpha_1 t} + (\alpha_2 - k_4)e^{-\alpha_2 t}\} \otimes Cp(t)\right]}{\frac{k_2 + k_3}{\alpha_2 - \alpha_1}(e^{-\alpha_1 t} - e^{-\alpha_2 t}) \otimes Cp(t)},$$

$$\alpha_1 = \frac{1}{2}\{k_2 + k_3 + k_4 - \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2k_4}\},$$

$$\alpha_2 = \frac{1}{2}\{k_2 + k_3 + k_4 + \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2k_4}\}, \quad \text{Eq. 12}$$

where Cp is the plasma glucose level (mg/dL), LC is the lumped constant and Ci(T) is the radioactivity of FDG in the brain at time T and $\otimes$ $C_p(t)$ denotes the convolution of plasma activity of FDG. k_1, k_2, k_3 and k_4 are the rate constants for carrier-mediated transport of FDG from plasma to tissue, for carrier-mediated transport back from tissue to plasma, for phosphorylation by hexokinase and for FDG-6-phosphate hydrolysis by glucose-6-phosphatase, respectively.

The k values were fixed as follows (k_1 ml/min/g; k_2, k_3 and k_4 min^{-1}): $k_1 = 0.102$, $k_2 = 0.13$, $k_3 = 0.062$ and $k_4 = 0.0068$ (*5*). The LC was also fixed at 0.42 (*5*). The estimated individual input function with BSA correction, C'p(t) = IFsimbsa, was calculated with Equation 10. These parameters and Equation 12 were used to calculate, on a pixel-by-pixel basis, the CMRGlc estimated with BSA (CMRGlc.simbsa). CMRGlc.simbsa was compared with CMRGlc calculated with the measured input function (CMRGlc.real) on a region-of-interest (ROI) basis. ROIs were placed on the frontal, temporal, occipital, parietal cortex centrum semiovale, cerebellum, basal ganglia and thalamus bilaterally in both images. Identical ROIs were used to calculate CMRGlc.real and CMRGlc.sim. As shown in Equation 12, CMRGlc and tissue activity are linearly related, and hence CMRGlc.sim against CMRGlc.real is linearly related (Fig. 1). Sixteen pairs of the values of CMRGLc for each subject were plotted to obtain the slope (A) and y-intercept (B) of the regression line to calculate the percentage error of estimation with the following equation:

% error of estimation of CMRGlc =

$$\left|A + \frac{B}{CMRGlc.real} - 1\right| \times 100. \quad \text{Eq. 13}$$

Note that the percentage error of estimation of CMRGlc depends on the value of CMRGlc.real. The percentage error of estimation in gray and white matter was obtained for the values of 7.3 and 3.4 mg/min/100 g CMRGlc.real, respectively, and are reported as the mean normal values (*5*).

Standardized Input Function with Body Weight Correction

The SIF with a correction for BW was calculated by the same procedure used for SIF with BSA correction. Abbreviations for the BW correction are as follows: SIFbw = standardized input function with BW correction; IFsimbw = simulated input function with BW correction; $AUC_{IFsimbw}$ = area under the curve obtained from IFsimbw; and CMRGlc.simbw = CMRGlc calculated with IFsimbw.

Statistical Analysis

The *t* test was used for the comparison of body habitus and plasma glucose levels of patients in groups 1 and 2. One-way factorial analysis of variance was used for the comparison of CMRGlc.real, CMRGlc.simbsa and CMRGlc.simbw in each region in each patient. Percentage error of estimation is expressed as mean ± SD. Statistical significance was defined as $P < 0.05$.

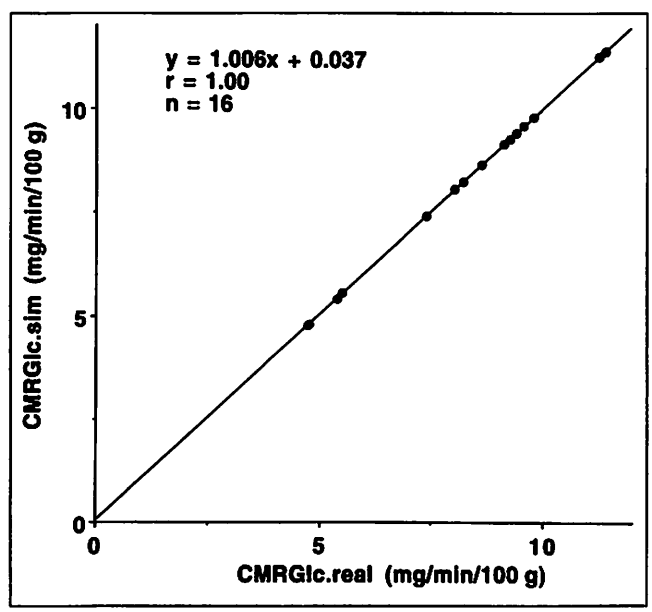

FIGURE 1. Deviation between CMRGlc.real and CMRGlc.sim. All 16 points of ROI values are on regression line.

RESULTS

There was no significant differences in body habitus or plasma glucose levels between groups 1 and 2 (height P = 0.32, weight P = 0.35, BMI P = 0.08 and plasma glucose level P = 0.17).

The coefficient of variation (CV) at each sampling time point in the first 5 min after injection of FDG varied more than 40%. From 5 to 60 min, the CV ranged from 11.5% to 13.0% in SIFbsa (Fig. 2) and from 14.4% to 18.6% in SIFbw. Percentage error of estimation of the AUC in group 2 was 3.5% ± 2.2% with BSA correction and 3.7% ± 2.9% with BW correction.

There was no significant difference between CMRGlc.real and CMRGlc.simbsa or CMRGlc.simbw in each region in any of the patients ($P > 0.1$). Percentage error of estimation of CMRGlc with BSA was 2.9% ± 1.9% in gray matter and 3.4% ± 2.2% in white matter, and with BW the percentage error of estimation was 3.9% ± 3.3% in gray matter and 4.7% ± 3.4% in white matter (Fig. 3).

DISCUSSION

For the precise calculation of CMRGlc with an autoradiographic method, based on the model of Sokoloff et al. (*1*), a steady state of glucose concentration is a basic assumption. That is why our patients fasted for at least 6 h before the PET examination. Under this condition, the plasma clearance rate of FDG is constant across subjects (*8*), and, therefore, a constant shape of input function can be safely assumed. An insulin clamp procedure used in cardiac FDG studies showed accelerated plasma clearance of FDG (*13*), which was attributed mainly to increased tissue uptake of FDG by induction of the glucose transporter. Exercise is known to increase the glucose uptake in striate muscles. Although the plasma glucose concentration does not affect the plasma clearance of FDG (*8*), brain FDG uptake is decreased by acute hyperglycemia (*14*). Therefore, the fasting state is recommended for optimal evaluation of cerebral glucose metabolic rate.

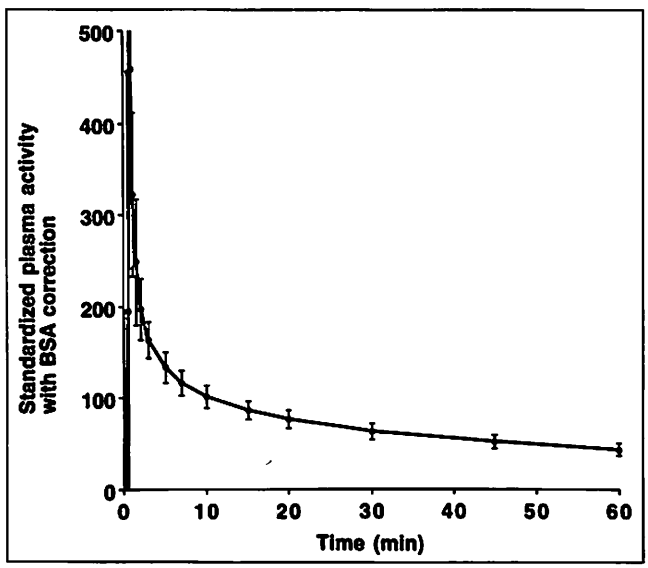

FIGURE 2. SIF with BSA correction. Error bars show SD of each sampling point.

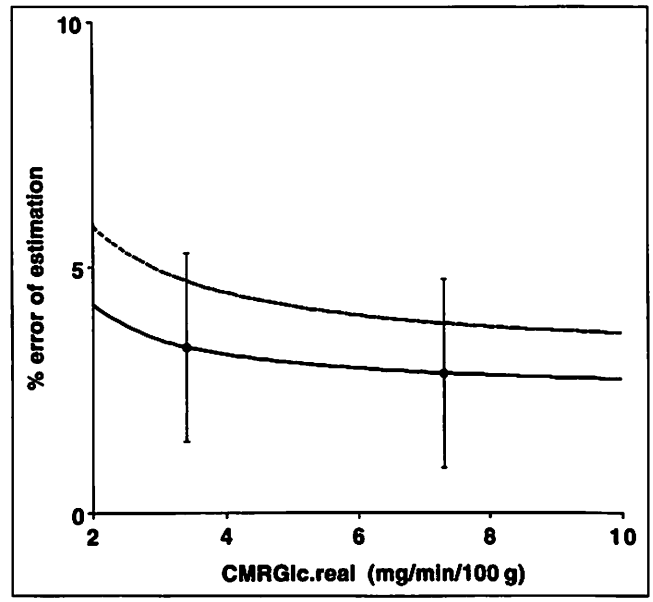

FIGURE 3. Averaged percentage error of CMRGlc.simbsa (solid line) and CMRGlc.simbw (dashed line) against CMRGlc.real in group 2. Two points represent mean ± SD of percentage error of estimation at 7.3 and 3.4 mg/min/100 g CMRGlc.real.

In other methods for the noninvasive estimation of input function (*6,7*), the shape of the input function commonly was assumed to be the same across subjects. These methods calibrate the population-based standard input function to the individual input function using the measured plasma FDG concentration. With the same assumption of constant shape of the input function, we attempted the same calibration, but using instead the ID per BM. This is possible because the ratio of BM to initial distribution volume is relatively constant (*8*). Because the ID divided by the initial distribution volume is the initial plasma FDG concentration, given the steady state is established between intra- and extravascular space (*8*), our approach is an extension of the previous methods (*6,7*) and is subject to similar limitations. For example, compartment analysis with dynamic data for determination of rate constants would be difficult, as shown by Takikawa et al. (*6*). A specific issue concerning our methods is the estimation of the initial distribution volume of FDG by BM. The distribution of FDG is much less in fatty tissues than in lean body mass (*15*), and the distribution volume is smaller. Because BSA is a better indicator of lean BM than BW, particularly in obese subjects (*16*), the proposed method based on BSA should be better for estimating input function. The accuracy of our estimation of CMRGlc by either BSA or BW is similar, because the population we examined did not include extreme body habitus. Although BSA-based calculation is expected to estimate CMRGlc better than BW in a population with a wide variety of body types, the superiority should be confirmed by future studies.

The shape of the normalized input functions in group 1 varied across subjects for up to 5 min, because of fluctuation between the intra- and extravascluar components of the FDG pool. The manual injection of FDG and intermittent sampling of arterial blood may contribute to the variation in the early phase of the input function. Nevertheless, differences in CMRGlc were small, because the autoradiographic method is less likely to be affected by errors in the measurement of the input function (*6*). CMRGlc values are dependent on the AUC of the input function at the time of scanning (*6,17*), instead of its rate of change (*18*). CMRGlc values obtained from studies with slow FDG injection (for 3 min) and bolus injection agree well (*19*), supporting the notion that the style of injection does not affect the results (*7*). Moreover, this study showed that the percentage error of CMRGlc is almost equal to the percentage error of the AUC. Hence, evaluation of the AUC is essential in the noninvasive method. Takikawa et al. (*6*) found that the AUC was virtually proportional to the mean plasma FDG activity of arterial blood sampled at 10 and 45 min after injection. They also reported that the difference in CMRGlc calculated from the real input function and from the estimated input function calibrated with two-point arterial blood sampling was 0% ± 0.2%. Without arterial sampling, our method provided a good estimation of the AUC (% error 3.5% ± 2.2% with BSA correction in group 2), as well as the CMRGlc (2.9% ± 1.9% in gray matter and 3.4% ± 2.2% in white matter). The larger percentage error of CMRGlc given by our method is probably related to the fact that estimation of the AUC is less accurate than that provided by Takikawa et al. (*6*). Huang et al. (*5*) reported that CMRGlc in healthy volunteers was 7.30 ± 1.18 mg/min/100 g in gray matter and 3.41 ± 0.64 mg/min/100 g in white matter, and the CVs were 16.2% in gray matter and 18.8% in white matter. The errors yielded by our method were within this range of variation, and the estimated CMRGlc and the measured CMRGlc were not significantly different. Considering the merits of avoiding blood sampling, our results are thought to be acceptable in the clinical situation.

Application of the noninvasive method to diabetic populations is another issue. Eberl et al. (*7*) reported that in diabetic patients, CMRGlc calculated with an estimated input function obtained from nondiabetic patients and calibrated with arterialized venous samplings, did not lead to an increase of error. Because no patient in this study was diabetic, whether the proposed method may be applicable to patients with diabetes must be determined by studies on such patient populations.

CONCLUSION

The measurement of CMRGlc performed without blood sampling in the fasting state provides acceptable accuracy in clinical settings.

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