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# Quantitative PET cerebral glucose metabolism estimates using a single non-arterialized venous-blood sample

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The purpose of this study is to develop a method of quantitating the cerebral metabolic rate of glucose (CMRglc) by positron emission tomography using a population-based heated venous curve and one-point sampling from a non-heated vein, i.e. that can avoid arterial puncture. ***Methods:*** We conducted this study on 17 subjects with a mean age of 61 ± 9 years. A time-concentration curve as an input function was obtained by sampling 24 blood samples, from the heated left hand vein, one before and the others after intravenous injection of 259 MBq of F-18-fluorodeoxyglucose into the right cubital vein. A non-heated venous sample was also obtained from the right cubital vein. ***Results:*** The population-based input function was calculated by averaging time-concentration curves from the first 7 subjects. A single sample obtained from 10 other subjects from 7.5 to 20 minutes and 35 and 40 minutes after injection predicted input function well with an error of less than 4.5%. The radioactivity in the non-heated 40 minutes' sample was 1.7 ± 2.9% higher than in the heated vein. When we calibrated the population-based curve using the non-heated venous samples at 40 minutes in 10 subjects, the calculated CMRglc values were 1.3 ± 5.4% lower than the actual values. ***Conclusions:*** Non-heated venous one-point sampling and the population-based curve can decrease the complexity of the procedures and the manpower required, and also make the FDG study less invasive, without a significant increase in measurement error.

**Key words:** $^{18}$F-FDG, PET, cerebral metabolic rate of glucose, input function, venous sampling

## INTRODUCTION

TOMOGRAPHIC MEASUREMENT of local cerebral glucose metabolism (CMRglc) by positron emission tomography[1] has been used for more than 20 years in patients with dementia,[2,3] cerebrovascular disease,[4] brain tumor,[5,6] epilepsy[7] and so on. To estimate CMRglc by the three-compartment tracer model originally developed by Sokoloff et al.,[8] however, it is necessary to measure the arterial fluorine-18 fluorodeoxyglucose ($^{18}$F-FDG) time-concentration curve during the entire period of radioisotope uptake into the brain as an input function. To avoid the invasiveness of the arterial puncture and the time and manpower required to collect and process the samples,[9] a hand vein was warmed, and 'arterialized' venous blood was taken as an alternative to arterial blood.[1,10] This method has been validated in four human subjects[1] as a substitute for the arterial curve. It makes the procedure less invasive but still needs complex procedures associated with the collection and processing of numerous blood samples. Recently, a method has been developed to estimate the input function by calibrating a population-based arterial blood curve with one or two-point sampling.[11,12] This method requires arterial cannulation and the measurement of actual input function to obtain the standard arterial blood curve in advance.

To avoid the invasiveness associated with cannulation of the artery, we obtained the standard input function from the heated vein. We also avoided the discomfort of puncturing the small heated hand vein, by sampling one specimen from the non-heated cubital vein.

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## MATERIALS AND METHODS

This study was conducted on 17 subjects (9 men and 8 women, mean age: 61 years ± 9, range: 46–79 years). They consisted of 11 patients with cerebral infarction, 2 with Alzheimer's disease, 1 with Parkinson's disease, 1 with spinocerebellar degeneration, 1 with corticobasal degeneration, and 1 with epilepsy. Written informed consent was obtained from each subject. CMRglc was measured in all of the subjects by using a positron emission tomograph (ECAT EXACT 47/921, Siemens/CTI). A right cubital vein was cannulated to inject the radioisotope and to sample blood. The left hand was heated by wrapping it in an electrical warmer with the thermostat set at 44°C, and the left hand vein was cannulated for sampling heated venous blood. After heating the left hand for at least 5 minutes, 259 MBq of $^{18}$F-FDG in 2.5 m*l* of saline followed by 5 m*l* of saline was injected into the right cubital vein by an autoinjector. Twenty-four 1-m*l* blood samples were obtained from the heated left vein, immediately before the injection, and 15, 30, 45 seconds, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 7.5, 10, 13, 16, 20, 25, 30, 35, 40, and 62 minutes after the injection, respectively. The times of the beginning and the end of each sampling were recorded, and the midtime of the beginning and the end of sampling was thought to be the sampling time. Two successive blood samples were also obtained from the right cubital vein 40 minutes after the injection, the first for the serum glucose concentration and the second for radioactivity to compare the heated and non-heated venous blood. To avoid contaminaion of the blood sample collected from the right side by highly active $^{18}$F-FDG, the catheter was flushed with 5 m*l* of saline 10 minutes after injection and also immediately before each sampling at 40 minutes. Blood samples were centrifuged, and radioactivity was measured in 200 $\mu l$ of plasma with a well counter. PET scanning was performed for 15 minutes between 45 and 60 minutes after the injection. Transmission scans were not performed in this study. Attenuation correction and reconstruction was achieved by using a contour-fitting algorithm.[13] Image processing and region of interest (ROI) analysis were performed by the operating software on ECAT 47 workstation, and all of the statistical analyses were done by STATVIEW on a personal computer (Power Macintosh 8100/80AV).

*Population-Based Heated Venous Curve*

We normalized the decay-corrected heated venous curve from the first seven subjects (subject no. 1 to 7) so that the time integrals of the seven activity curves (area under the curve; AUC) would be the same. We then calculated the population-based heated venous curve by averaging the activity and also the sampling time in every time point of 7 curves. The obtained population-based heated venous curve is shown in Figure 1.

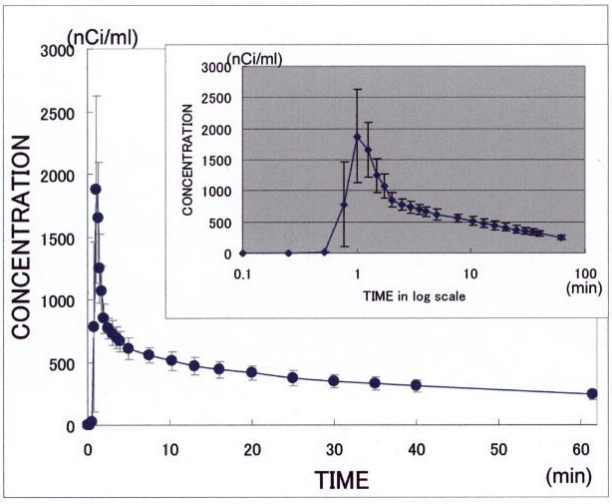


**Fig. 1** Population-based heated venous curves. The population-based heated venous curve was obtained by averaging seven normalized heated venous curves from subject no. 1 to 7. This curve, expressed as mean ± S.D., is decay-corrected for sampling time. The same curve except with the horizontal scale in logarithm is shown to clarify the initial part of the curve.

*Calculation of the Estimated Input Function*

The estimated input functions were calculated from the next 10 subjects (no. 8 to 17) by scaling the population-based curve with the ratio of actual radioactivity taken at time $i$ from the $j$-th subject to the standard radioactivity of the population-based curve at time $i$, by the following equation:

$$C_{ij}(t) = C_p(t) \times A_{ij} / C_p(i)$$

where $i$ = time at which the blood samples for scaling are drawn, $C_{ij}(t)$ = estimated input function of the $j$-th subject calibrated by the activity at time $i$, $C_p(t)$ = population-based heated venous blood curve, and $A_{ij}$ = FDG activity in the heated venous sample drawn at time $i$ from the $j$-th subject, and $C_p(i) = C_p(t)$ at time $i$. Fourteen estimated input functions were calculated in every subject (no. 8 to 17) by different calibrating factors obtained from 1.02 to 61.5 minutes. We then calculated AUCs from the actual heated venous curve and the estimated input functions.

*Sample Best Predicting Actual Input Function*

We identified the sample that best predicted the AUC from the heated vein in 10 subjects (no. 8 to 17) by calculating the correlation coefficients between AUC and radioactivity in heated venous samples collected at various times. In order to evaluate the accuracy of the predictions, the difference between the AUC in the actual heated vein and the AUC in the estimated input function calibrated by activity at the various sampling times was then calculated thus:

$$\text{difference} = \frac{1}{10}\sum_{j=1}^{10}\frac{|\text{AUC}_j \text{ actual} - \text{AUC}_j \text{ estimated}(i)|}{\text{AUC}_j \text{ actual}} \quad (1)$$

where $\text{AUC}_j$ actual = AUC in the actual heated vein of the $j$-th subjects and $\text{ACU}_j$ estimated($i$) = AUC in the estimated input function of the $j$-th subject calibrated by the activity at time $i$.

*Difference in Activity between Heated and Non-Heated Venous Blood*

In attempting to develop the non-heated venous sampling method, however, several factors in addition to accuracy had to be taken into consideration. For example, the subjects must be kept as steady as possible during the uptake period. Also, it is more convenient to collect blood samples when the subject is lying in bed in the PET room just before the PET scan, than when sitting in the chair in the waiting room. Taking these factors into account, we took the samples from the non-heated vein at 40 minutes. The difference in activity between samples collected 40 minutes after injection from the heated and non-heated vein was compared in the 17 subjects.

*CMRglc Values*

In each of 10 subjects (subject no. 8–17) not used to estimate the population-based standard venous curve, two estimated input functions were calculated using the 40-min samples from the heated vein and non-heated vein, respectively. CMRglc values were calculated with the autoradiographic method.[1,8] Three sets of CMRglc images, each consisting of 47 slices, were calculated in these 10 subjects, one using the actual input function (CMRglc(A)), one using the estimated input function calibrated by the 40-min sample from the heated vein (CMRglc(H)), and one using the estimated input function calibrated by the non-heated 40-min sample (CMRglc(NH)). CMRglc values were obtained for 23 ROIs from three sets of CMRglc images in every subject. Every ROI was placed in the same position of the same slice through all three sets of CMRglc images in a given individual. Mean CMRglc values from the 23 ROIs were compared between the three sets of CMRglc images.

## RESULTS

*Determination of the Sample Best Predicting the AUC of the Blood Curve*

The correlation coefficients between the AUC and the radioactivity in the actual heated-venous samples taken between 1.02 and 61.5 minutes after the injection are shown in the middle column of Table 1. The samples collected between 16 and 40 minutes had high correlation coefficients ≥ 0.973 with the AUCs. The highest coefficient was between the 35-min sample and the AUC (r = 0.983), followed by the 40-min sample (r = 0.979). Table 1 also shows the mean of the absolute value of difference between the AUCs of the actual heated venous curve and those of the estimated input function calibrated by the activity at the various sampling times between 1.02 and 61.5 minutes, as defined by the equation.[1] Although there is some fluctuation of difference with sampling times, the samples taken between 7.5 and 20 minutes and at 35 and 40 minutes were good predictors of the AUC of the blood curve, with differences between 2.9% and 4.5%.

**Table 1** Correlation coefficients between heated venous activity and AUC, and difference between AUCs of the actual heated venous curve and of estimated input function

| sampling time (min) | correlation coefficient | difference |
|---|---|---|
| 1.02 | 0.607 | 0.448 ± 0.309 |
| 2.97 | 0.961 | 0.050 ± 0.041 |
| 4.00 | 0.944 | 0.044 ± 0.043 |
| 5.02 | 0.951 | 0.055 ± 0.046 |
| 7.57 | 0.960 | 0.045 ± 0.028 |
| 10.3 | 0.958 | 0.029 ± 0.033 |
| 13.0 | 0.950 | 0.044 ± 0.035 |
| 16.1 | 0.973 | 0.040 ± 0.024 |
| 20.0 | 0.974 | 0.039 ± 0.025 |
| 25.0 | 0.974 | 0.053 ± 0.027 |
| 30.0 | 0.977 | 0.046 ± 0.033 |
| 35.0 | 0.983 | 0.033 ± 0.027 |
| 40.1 | 0.979 | 0.041 ± 0.034 |
| 61.5 | 0.915 | 0.060 ± 0.054 |

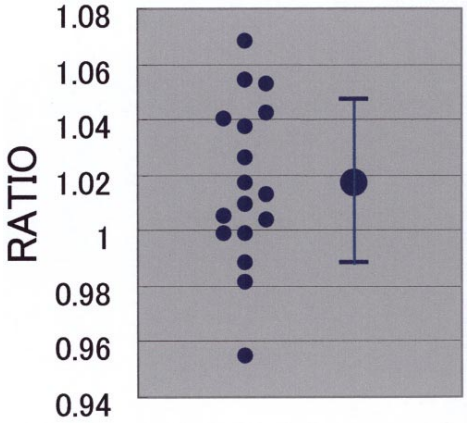


**Fig. 2** Ratio of radioactivity on the non-heated side to the heated side at 40 minutes.

*Difference in Activity between Heated and Non-Heated Venous Blood*

Figure 2 shows the ratio of radioactivity on the non-heated side to the heated side at 40 min. Activity is 1.7% higher on the non-heated side than on the heated side, with a standard deviation of 2.9%. This also indicates that flushing the catheter twice (once after injection and once immediately before sampling) is sufficient to avoid contamination.

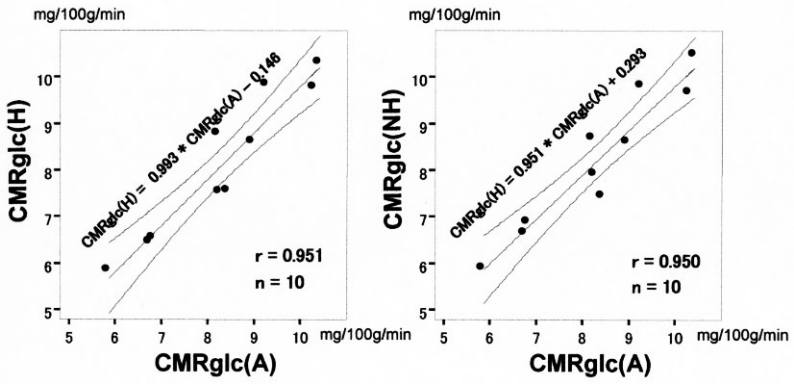


**Fig. 3** Relationship between mean CMRglc values from the actual venous curve and from the estimated input function. Relationship between mean CMRglc values using the actual heated venous curve (CMRglc(A)) and CMRglc values using the estimated input function using heated venous samples (CMRglc(H), *left*) and using non-heated venous samples (CMRglc(NH), *right*) are shown. Solid lines indicate regression line, and curved lines indicate 95% confidence interval. Regression equations are, CMRglc(H) = 0.993 × CMRglc(A) − 0.146, and CMRglc(NH) = 0.951 × CMRglc(A) + 0.293, respectively.

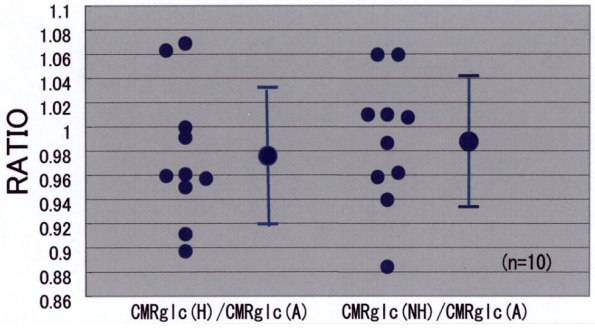


**Fig. 4** Ratio of mean CMRglc values from estimated input function to values from the actual venous curve. Ratio of mean CMRglc values using estimated input function from heated venous samples (CMRglc(H), *left*) and non-heated venous samples (CMRglc(NH), *right*) to mean CMRglc using the actual heated venous curve are shown.

*CMRglc Values*

Figure 3 shows the relationship between the mean CMRglc(A) values and CMRglc(H) values (*left*) or CMRglc(NH) values (*right*). The correlation coefficients are 0.951 and 0.950, respectively. Figure 4 shows the ratio of CMRglc(H) (*left*) or CMRglc(NH) (*right*) to CMRglc(A). The CMRglc(H) value was 2.5% lower than the CMRglc(A) value, with a standard deviation of 5.7% (*left*). When we used the non-heated venous sample to calibrate the input function, the CMRglc(NH) value was 1.3% lower than the CMRglc(A) value, with a standard deviation of 5.4% (*right*).

## DISCUSSION

Our data showed that it is possible to estimate the input function with errors of less than 4.5% of AUC by using heated venous samples collected between 7.5 and 20 minutes and at 35 and 40 minutes. The 40-min sample yielded the second best correlation coefficient with AUC. Wakita et al.[12] found the best sample with the most accurate estimation of the input function at 12 minutes after injection. The difference in the result might be due to a difference in the shape of the arterial curve and arterialized venous curve.[12] Wakita et al.[12] used 120 patients to obtain the mean blood curve while we used 7 patients. They showed a very high correlation coefficient of 0.9982 between the arterial activity at 12 minutes and AUC. Our data show a smaller but still high correlation coefficient (0.979) between estimated input function and AUC. Our data, we think, are still applicable to the routine clinical use of the PET scan.

Our data also indicate that 40 minutes after the injection of $^{18}$F-FDG, heated and non-heated venous blood contain almost the same radioactivity, with a standard deviation of 2.9%. Phelps et al.[1] reported that since a steady state is reached after injection of FDG, the arterial and non-heated venous concentrations parallel each other. According to figure 9 in their paper, non-heated venous activity are almost the same as the arterial values from 40 minutes after injection onward. This equality does not hold, however, in the situation of increased glucose uptake such as during euglycemic-hyperinsulinemic clamp.[14]

Although it is reported that the arterial integrated value is well estimated by the one point venous sampling with the percentage error of 3.64% by Wakita et al.[12] the percentage error of CMRglc by the one point venous sampling has not been reported. Our data showed that CMRglc values obtained by non-heated venous sampling were 1.3% lower than the actual values, with a standard deviation of 5.4%. Takikawa et al.[11] reported that the two-

point sampling from the heated vein yields a difference in CMRglc of 0.9 ± 2.5%, which is smaller than our results. The larger difference and standard deviation in our study may be because we calibrated input function by only one sample instead of two.

The test-retest variability of parameters measured by PET is reported to be between 4 to 14%.[4,15–17] Reported coefficients of variation of repeated measurements of CMRglc on the same day are 5.5% to 8.7% for gray matter structures and 9.7% to 14.0% for white matter structures [15] over the 2 hour period, or 8 % to 9 % over the half day.[16] The differences in cerebral blood flow and cerebral metabolic rate of oxygen within 1 hour are 4 to 10%,[4] and the standard deviation of uptake constant for $^{18}$F-fluorodopa[17] is 8.7%. The mean ± standard deviation of −1.3 ± 5.4% in our estimates using the non-heated 40-minutes sample is within the range of test-retest variability, and the one-point calibration method does not seem to affect significantly the accuracy of PET quantitation.

It is known that there is a difference between arterialized venous time activity curve and arterial curve. It is theoretically better to use an arterial curve as the standard. We used, however, a population-based heated venous curve as the standard in our study in order to avoid invasiveness. This is based upon the fact that the heated venous curve has been validated in four human subjects[1] as a substitute for the arterial curve.

We calculated the CMRglc value by the autoradiographic strategy. The one-point calibration method with population-based curve is applicable only to the autoradiographic method, and not to the kinetic approach. Our estimation may be erroneous if the shape of the input function is different from the population-derived curve. Such situation may occur in case of disturbances of cardiovascular function, such as heart failure, or diabetes mellitus with a gentler slope due to insufficient insulin action or a steeper slope because of glucosuria. On the other hand, this method has good indications in subjects without such disorders. This method is already applied to the subjects who have undergone the "brain check-up" program in our institute for detection of asymptomatic brain diseases. Follow-up studies on the same subjects may also be a good indication.

Our one-point calibration method using non-heated venous samples makes the $^{18}$F-FDG PET procedure less invasive. The advantages of this method are as follows. First, it does not require cannulation of a small hand vein, so that this method can be used in subjects who are uncooperative with hand heating or cannulation of the small hand veins. Second, the subject is not necessarily kept at the heating devices during the uptake period, which in turn makes the activation study under various conditions, or even during exercise possible. Third, this method can decrease the manpower required for the PET study without increasing equipment, so that it is possible to perform CMRglc studies on many subjects on the same day. Fourth, another study such as whole-body scan for cancer screening can be done during the uptake period without increasing the radiation doses.

Recently the number of PET examinations undertaken to evaluate patients with dementia, cerebrovascular disease, brain tumor, epilepsy and various pathological states has been increasing. In our institute, whole-body PET is already used to screen for occult cancer and decreased cerebral metabolism at the same time.[18,19] The one-point calibration method for CMRglc using a non-heated vein may promote routine clinical applications.

## CONCLUSION

To measure CMRglc values by PET using the autoradiographic method, the one-point sampling from the non-heated vein and the population-based heated venous curve might be sufficient. This simple and less invasive procedure is applicable to clinical situations such as follow-up study, activation study, studies on uncooperative or demented subjects, studies on several subjects on the same day, or study with whole-body scan during the uptake period. Application to subjects with a possibly different shape of input function still needs further study.

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