—寄稿論文—

# The Study of the Calculation Method of the Regional Cerebral Blood Flow Using the Venous Blood and Development of the Software

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## I. Abstract

[Background] The accuracy of the microsphere (MS) technique for measurement of cerebral blood flow in $^{123}$I-labeled *N*-isopropyl-p-iodamphetamine (IMP) single-photon emission computed tomography (SPECT), which requires continuous sampling of arterial blood, has been recognized. In recent years, autoradiography (ARG) technique has been widely used despite its lower accuracy, because it requires only a single arterial blood sampling. [Material and methods] In the present article, we report an accurate method requiring less than 1-hour's rest followed by acetazolamide stress test that involves the less invasive venous blood sampling. The patient factors used for the analysis of the 77 patients included over-time changes in the SPECT cerebral blood flow and the radioactivity in the venous blood at 55 minutes after $^{123}$I-IMP injection. The SPECT cerebral blood flow was assessed based on 9 frontal images. In addition, the time-course of changes in the SPECT cerebral blood flow was also evaluated in 50 patients in whom only the resting cerebral blood flow was measured. [Results] A multiple regression analysis showed a high

**Table 1 The Breakdown of Patients**
**We got agreement from the purpose of this study from 54 men and 23 women, and, in the age group, as for the man is from 33 to 80 years old, a woman is from 40 years old to 84 years old.**

| SEX | Male 54 patients | Female 23 patients |
|---|---|---|
| Age | 33-80 y.o. (mean 63.5 y.o.) | 40-84 y.o. (mean 59.9 y.o.) |
| Arterial Stenosis/Occlusion | | 44 |
| *ICA Stenosis/Occlusion | | 27 |
| **MCA Stenosis/Occlusion | | 14 |
| ***VA-BA Stenosis/Occlusion | | 3 |
| Moyamoya disease | | 6 |
| Arteriovenous Malformation | | 3 |
| Post operation | | 24 |
| ****EC-IC Bypass | | 14 |
| *****CAS/CEA | | 3 |
| ******AN Clipping/Coil embolization | | 7 |

* ICA : Internal carotid artery
** MCA : Middle cerebral artery
*** VA-BA : Vertebral artery-Basal artery
**** EC-IC : External carotid artery-ICA : Internal carotid artery
***** CAS/CEA : Carotid artery stenting/Carotid endarterectomy
****** AN : Aneurysm

correlation (multiple correlation, R = 0.9963) between the regional cerebral blood flow measured using continuously sampled arterial blood and that measured in a single venous blood sample. The acetazolamide stress test was performed following a one-day rest using the split-dose method reported by Hashikawa et al: The estimated residual drug in the split-dose test was evaluated in 50 patients in our hospital in whom only the resting cerebral blood flow was measured to compare the results of single linear regression analysis and those of the 35-minute equilibrium analysis. The single linear regression analysis reported by Hashikawa et al is quite suitable for estimating the changes in the cerebral radioactivity. Our study suggests the one-day acetazolamide stress test using venous blood samples is valid for clinical application.

## II. Introduction

The clinical significance of radionuclide-based techniques for cerebral blood flow measurement has been established[1~10]. Measurement of the cerebral blood flow at rest and under drug stress plays an important role in the evaluation and treatment of clinical conditions involving the nervous system. There have been many reports of measurement of the cerebral blood flow by SPECT using various tracers. The standard method employed in Japan is the microsphere (MS) technique that involves the use of $^{123}$I-IMP and requires continuous arterial blood sampling[11~13].

However, the MS technique is very cumbersome in the clinical setting, and it' s posing a severe burden on those performing the examination. In addition, it requires continuous arterial blood sampling, which is a major disadvantage on account of the high invasiveness. In recent years, the table look-up (TLU) method and autoradiography (ARG), which require only a single arterial blood sampling, have come to be widely used because of the convenience[14~22]. In the present study, we evaluated the usefulness of a one-day test involving venous blood sampling, rather than arterial blood sampling, with a shortened rest time prior to the acetazolamide (ACZ) stress test, to reduce the procedural invasiveness and time constraint for both patients undergoing the examination and the staff performing the examination.

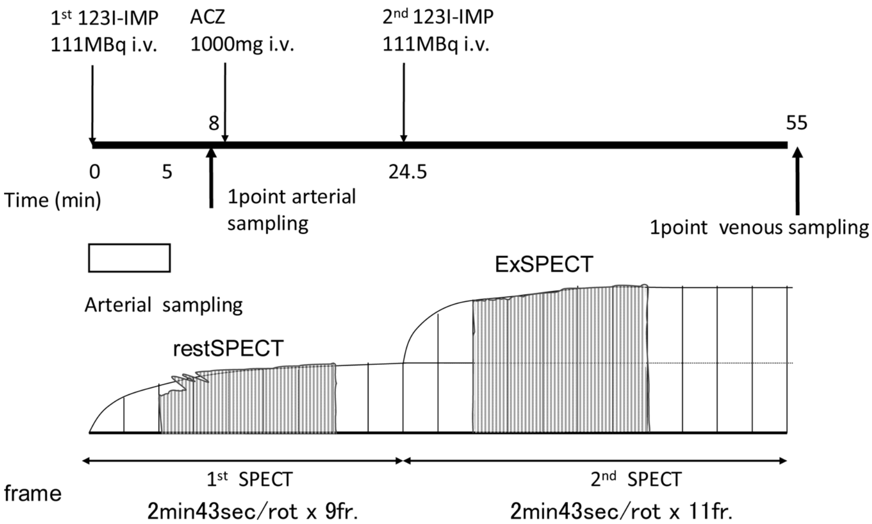



**Fig. 1 The protocol of the SPECT that I used for a calculation method of resional cerebral blood flow (rCBF) is the data collection condition that is the same as the protocol of the ARG method. I can apply this protocol to the rCBF calculation by the ARG method by adding a drawing blood maneuver from one point artery.**

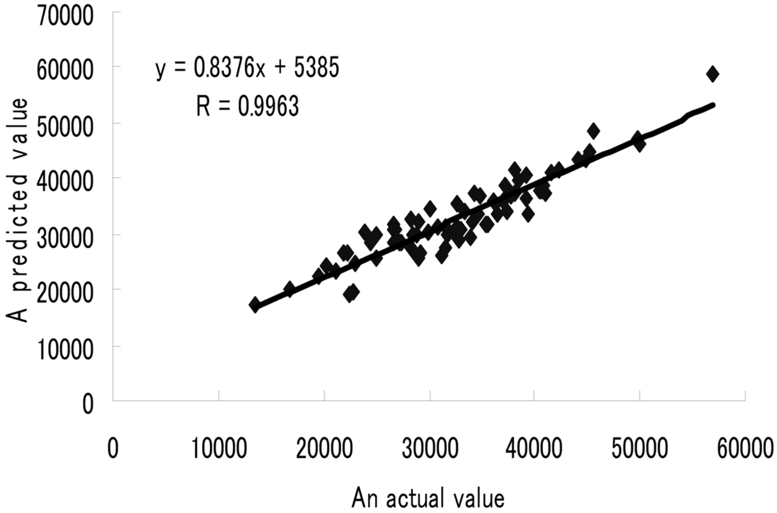
## III. Objectives

Several studies have reported less invasive methods for cerebral blood flow measurement by venous blood sampling[23~26]. Among these, the protocol reported by Mimura[25] appears to be the most convenient. Also the present study was conducted to establish a highly accurate method for the measurement of cerebral blood flow by improving this aforementioned protocol, and to evaluate the applicability of the one-day drug stress test for measurement of the cerebral blood flow reserve.

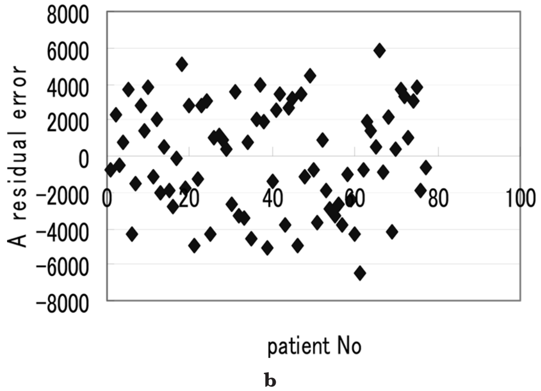
## IV. Material and methods

1. Subjects

The $^{123}$I-IMP SPECT was performed in a total of 77 patients (including pre- and postoperative patients and those being followed up) with cerebrovascular disorders from April 2007 to March 2008 (53 males [mean age, 63.5 years old ; range, 33 to 80 years old],




a




b

**Fig. 2 a : The X-axis expresses a real arterial blood count. The Y-axis is the result that performed a multiple regression analysis of a venous blood count and the count in the brain. The coefficient of both is 0. 837, and the graft is 5, 385. The coefficient of correlation is 0.9963. Both have very high correlation. b : The X-axis shows a patient number. The Y-axis shows the actual survey every patient and the residual substance of the prediction. There is not the example coming off greatly.**

24 females [mean age, 59.9 years old ; range, 40 to 84 years old]).

[**Table 1** : List of subjects]

2. SPECT

Triple-head SPECT system (Toshiba 9300A/D, with fanbeam collimators) ; the distance from each collimator to the rotating center was set at 132 mm (the minimum value). Images were obtained continuously under the following conditions : matrix 64 × 64, 6° × 20 steps × 20 frames × 3 directors (total, 6° × 1,200), and reconstructed to 4° × 1,800 ; the imaging time was 120°/75 seconds × 2 (120° reciprocation time for 150 seconds [2 minutes 30 seconds] (the actual reciprocation time was approximately 163 seconds [2 minutes 43 seconds] because of the angle [120 ± 3°] and the time lag for reversion). Arterial radioactivity estimation for measurement of the resting cerebral blood flow based on the changes with time of the cerebral SPECT values and in the radioactivity counts in venous blood samples : analyzed by the 50% threshold technique on frontal SPECT images.

3. Drugs

$^{123}$I-IMP 111 MBq × 2 and acetazolamide (ACZ) 1,000 mg

4. Procedure :

In all subjects, arterial blood was continuously sampled for 5 minutes after bolus intravenous injection of $^{123}$I-IMP 111 MBq. At 8 minutes after the injection, a single arterial blood sampling was performed and followed immediately by gradual intravenous injection of ACZ 1,000 mg. $^{123}$I-IMP 111 MBq was administered intravenously at 24.5 minutes after the ACZ injection, followed by a single venous blood sampling at 55 minutes after completion of the imaging. Cerebral radioactivity was measured at 9 time-points ; 1.3 minutes, 4.1 minutes, 6.7 minutes, 9.5

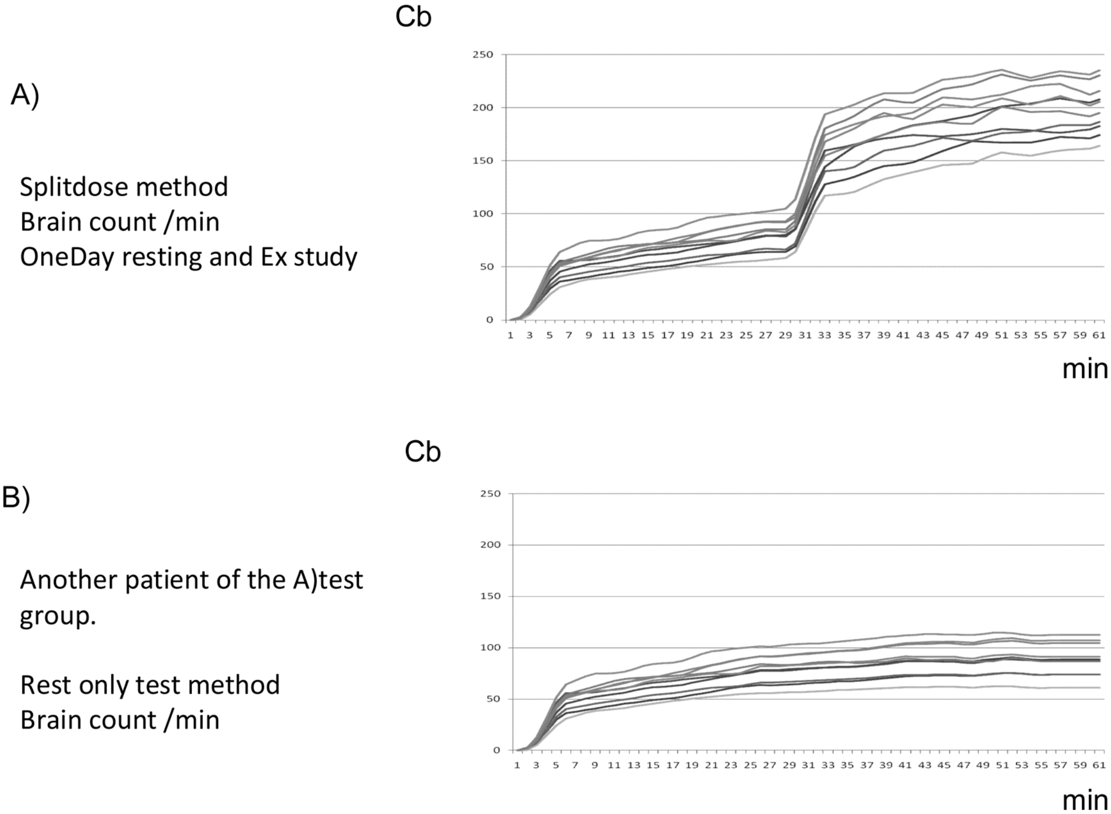



**Fig. 3 A) is the radioactivity amount of change in the brain by rest and the load Acetazolamide procedure in one day. In B), only as for the rest, it is the radioactivity amount of change in the brain by the laboratory procedure.**

minutes, 12.2 minutes, 14.9 minutes, 17.6 minutes, 20.3 minutes and 23.1 minutes.

[**Fig. 1** Test protocol]

5. Estimation of the residual amount of $^{123}$I-IMP in the one-day stress test

The residual amount of $^{123}$I-IMP used in the stress test was estimated according to the method proposed by Hashikawa et al[26]. Separately, the expected value was also calculated based on the hypothesis that the $^{123}$I-IMP level would even out at 35 minutes after administration[27].

## V. Results

1. The results of multiple regression analysis showed a high correlation (R = 0.9963) among the radioactivity counts (Ca) measured in the 5-minute continuous arterial blood samples collected using the MS method, those at each of the 9 time-points using the SPECT, and those estimated in the single venous blood sample at 55 minutes, after adjustments for the coefficient.

[**Fig. 2**. Correlation between the observed radioactivity count in arterial blood and the estimated radioactivity count in the venous blood]

[**Fig. 2a** : Graph showing the correlation between the observed radioactivity counts in 5-minute continuous arterial blood samples and those estimated in the single venous blood sample]

[**Fig. 2b** : Residual error between the actual cerebral radioactivity and the single regressive prediction]

2. Analysis of the changes with time of the resting cerebral radioactivity values estimated for the calculation of the cerebral blood flow under ACZ stress : The changes with time of the cerebral radioactivity values during the test are discussed. The second intravenous injection of $^{123}$I-IMP after the ACZ injection is included in the calculation of the (resting) cerebral radioactivity after the first $^{123}$I-IMP injection.

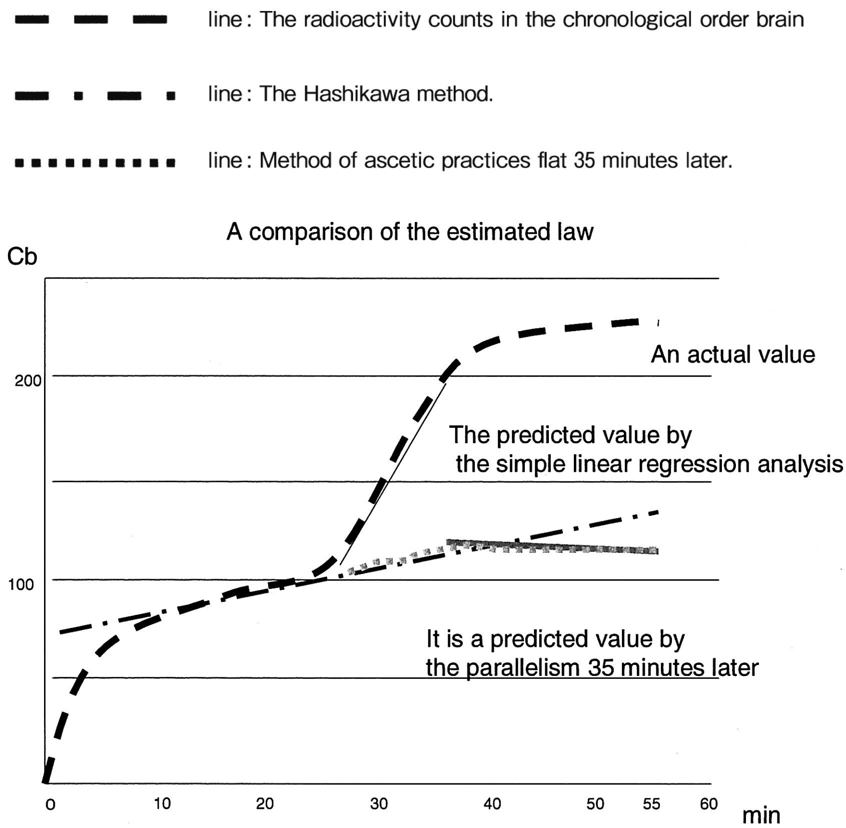



**Fig. 4 1st iv IMP expectation schematic view.**

As a result, inaccurate measurement of the resting cerebral radioactivity affects the measurement under ACZ stress.

[**Fig. 3a**: The changes with time of the cerebral radioactivity values in patients evaluated by the split-dose method]

Therefore, the changes with time of the cerebral radioactivity values were investigated in 50 patients who underwent the test for measurement of the resting cerebral blood flow alone.

[**Fig. 3b**: Changes with time of the cerebral radioactivity values in the resting cerebral blood flow test]

Currently, the calculation is performed according to the report by Hashikawa et al, however, the error becomes more pronounced when the shortened protocol is used. To avoid this possible error, the single regression method and arbitrary time series (temporal) (equilibrating) method were investigated. The single regression analysis was performed using 7 to 9 images according to the split-dose method. The expected value calculated based on the equilibration prediction that the cerebral radioactivity would even out at 35 minutes was compared to the results of the actual measurement. [**Fig. 4**: Estimation of the resting cerebral radioactivity for calculation of the cerebral blood flow under ACZ stress]

3. There was no significant difference in the residual error between the actual cerebral radioactivity and the single regressive prediction, or between the actual cerebral radioactivity and the 35-minute equilibrant prediction; however, the residual error was smaller in the single regressive prediction.

[**Fig. 5**: Comparison between the observed values and the values predicted by the single regressive method or 35-minute equilibration method]

Shows representative rCBF-SPECT images from the ACZtest-Group.

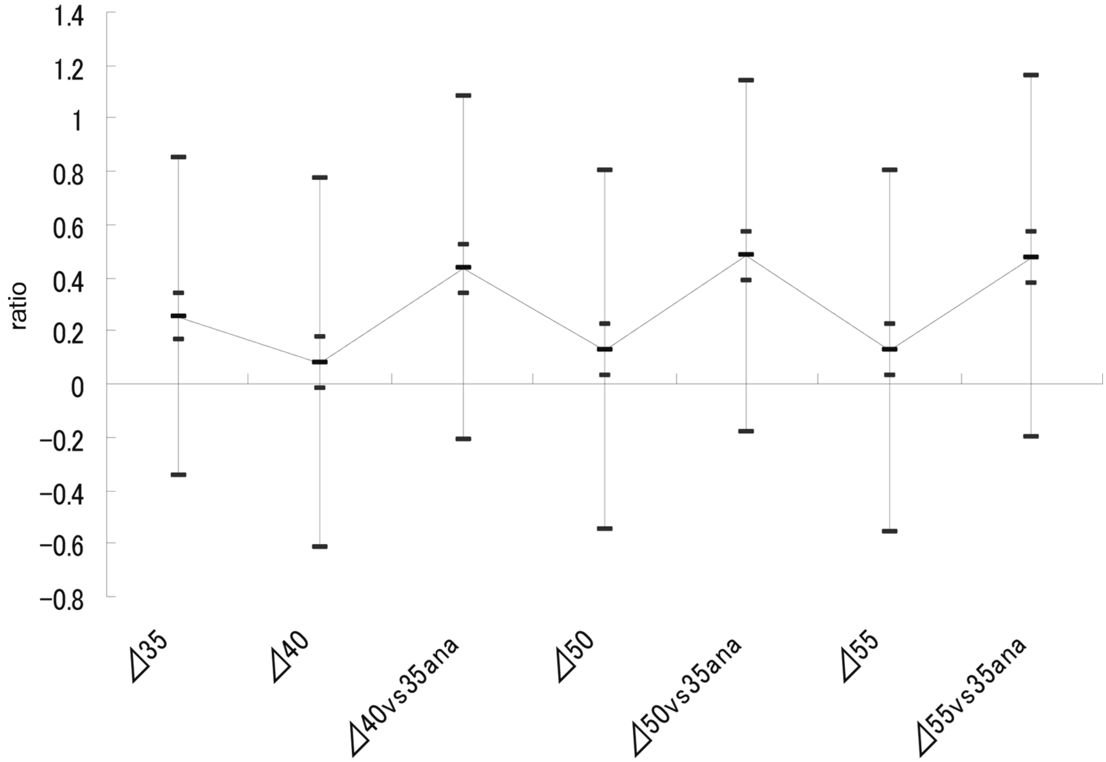



**Fig. 5 We compared Brain Count with a predicted value (simple linear regression analysis method and practices flat for 35 minutes) and the actual value of 40 and 45 minutes on the basis of a predicted value 35 minutes. Both did not have significant difference.**

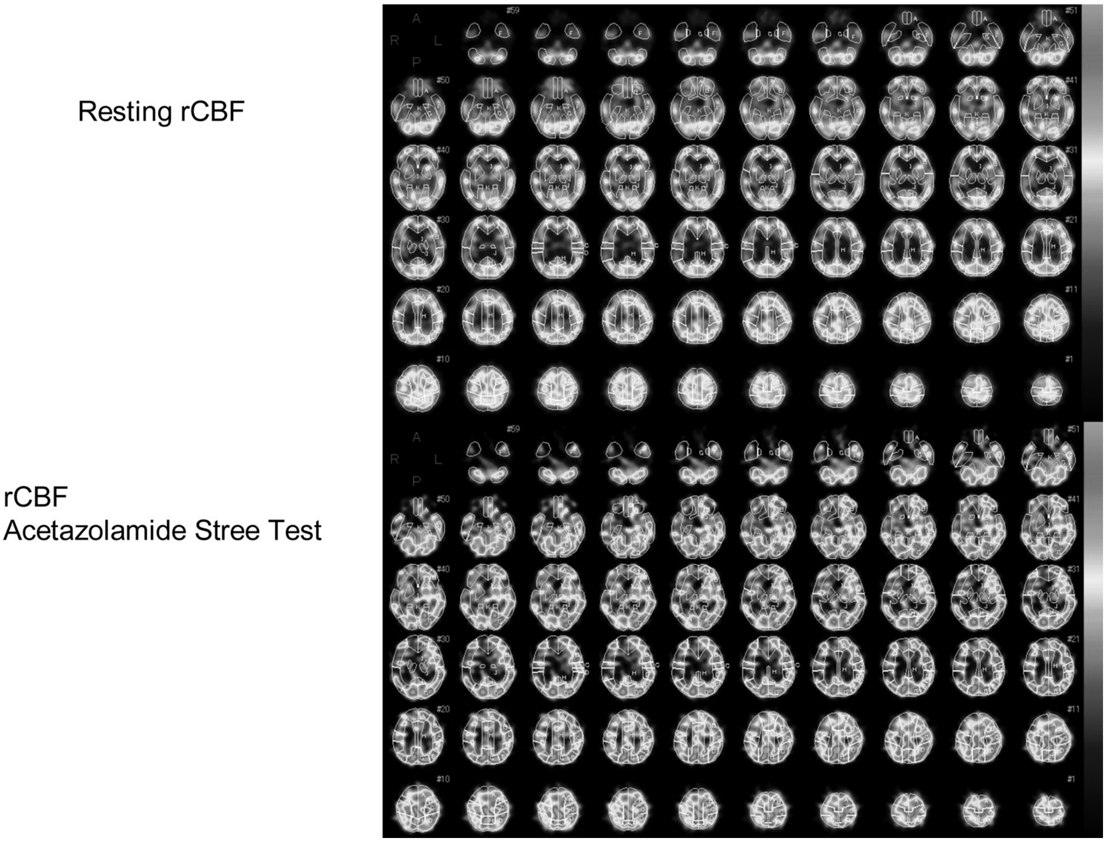



**Fig. 6　The case presentation.　The patient with One laterality cerebral infarction.　The result matches clinical manifestations.　We can evaluate brain circulation spare ability.**

[**Fig. 6** : Case presentation]

## VI. Discussion

The radioactivity counts in the continuously sampled arterial blood were estimated based on the over-time change in the cerebral radioactivity and the radioactivity count in a single venous blood sample collected at 55 minutes. The estimated radioactivity count (r = 0.9963) was higher than that reported by Mimura et al[25]. The stable overall radioactivity count may be attributed to the calculation of the cerebral radioactivity count : cerebral blood flow multiplied by the $^{123}$I-IMP plus the octanol extraction rate. While Mimura et al used approximately 30 minutes and a relatively late time-point after the SPECT as the factor points for the changes in the cerebral radioactivity, we used 9 time-points (1. 3 minutes, 4.1 minutes, 6.7 minutes, 9.5 minutes, 12.2 minutes, 14.9 minutes, 17.6 minutes, 20.3 minutes, and 23. 1 minutes). Since a 10-minute blood sampling time after $^{123}$I-IMP administration is associated with the least error in the ARG technique, the stable radioactivity counts may also be attributable to our evaluation method. In short, the results of our study support the causal model for the overall $^{123}$I-IMP concentration and the cerebral blood flow (an individual factor) proposed by Mimura et al, and our use of the 9 measurement time-points increased the accuracy.

The over-time change in the $^{123}$I-IMP concentration in the brain observed in the stress test is an integral of Ca. As a function, the changes with time are expressed as Ca × F, where F is a factor related to the cerebral blood flow, immediate octanol extraction

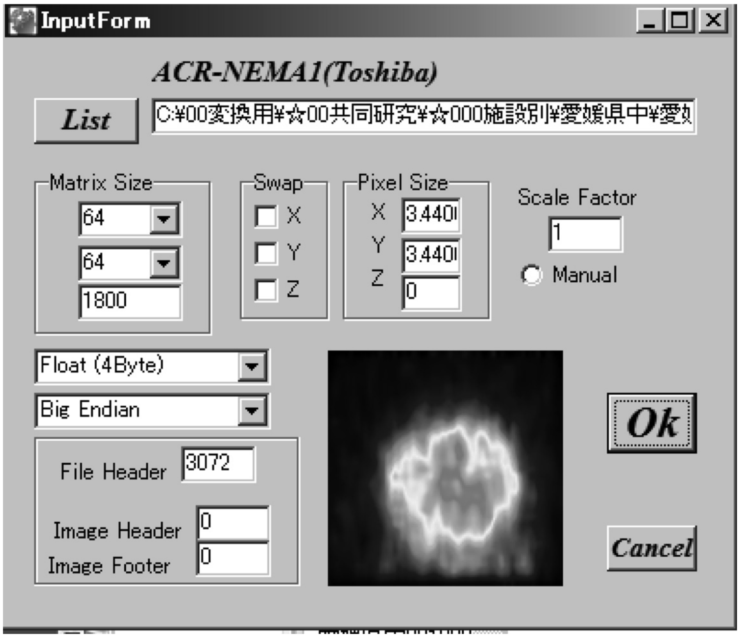



Fig. 7　You start it by an execute file.　You choose an image image targeted for analysis.　You confirm information to edit. You push the OK button.

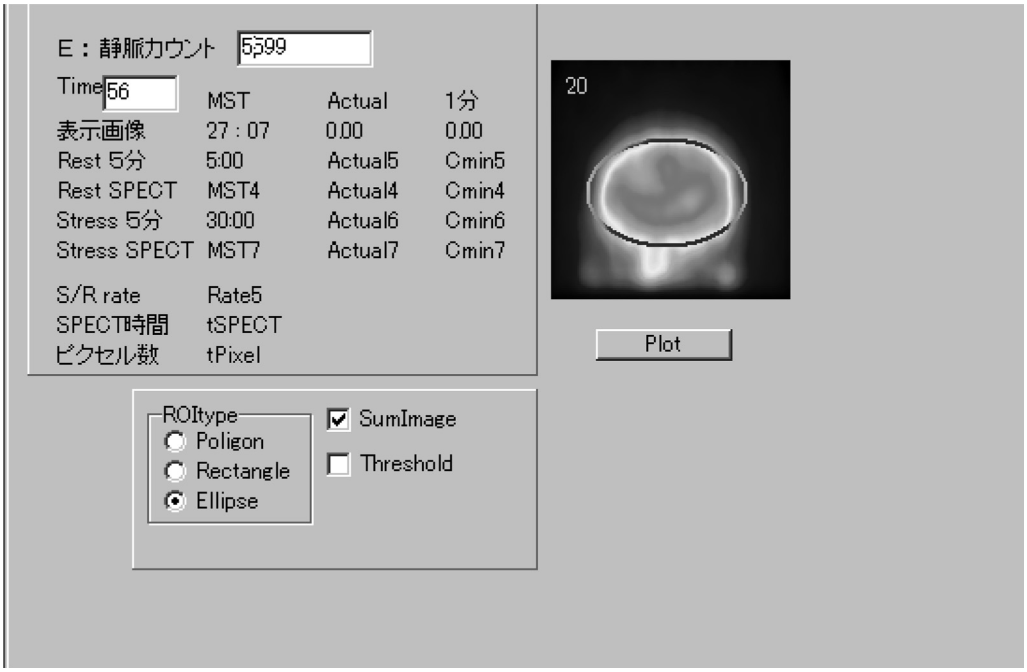



Fig. 8　You appoint time in a venous blood radioactivity count and a drawing blood timing.　You make target ROI to a brain image.

rate, etc. Our method allows estimation of SCa (5) and the basal regions of the second SPECT based on the factor, providing a pharmacokinetically simple model involving a test that can be completed within one hour.

Hashikawa et al used the single regression analysis to estimate the changes in the cerebral radioactivity in the one-day stress test, however, the radioactivity changes may reach equilibrium at 35 minutes after the intravenous injection of $^{123}$I-IMP, according to the experience. Our comparison showed that the single regressive prediction was associated with a smaller residual error. The split-dose method proposed by Hashikawa et al, which uses the actual change in the $^{123}$I-IMP concentration in individual patients, was shown to be sufficiently stable for clinical application.

## VII. Conclusion

The combination of single venous blood sampling and the split-dose method is non-invasive and convenient, and is thus beneficial for both the patients and for those who perform the examination.

The multiple regression analysis using the changes over time of the cerebral radioactivity count and radioactivity in the venous blood as variables showed a high correlation between the radioactivity in the arterial blood estimated from the radioactivity in a one-point venous blood sample and the actual radioactivity measured in continuously collected arterial blood samples, suggesting that our method is suitable for clinical application.

## VIII. SOFTWARE

We developed software for the reproducible im-

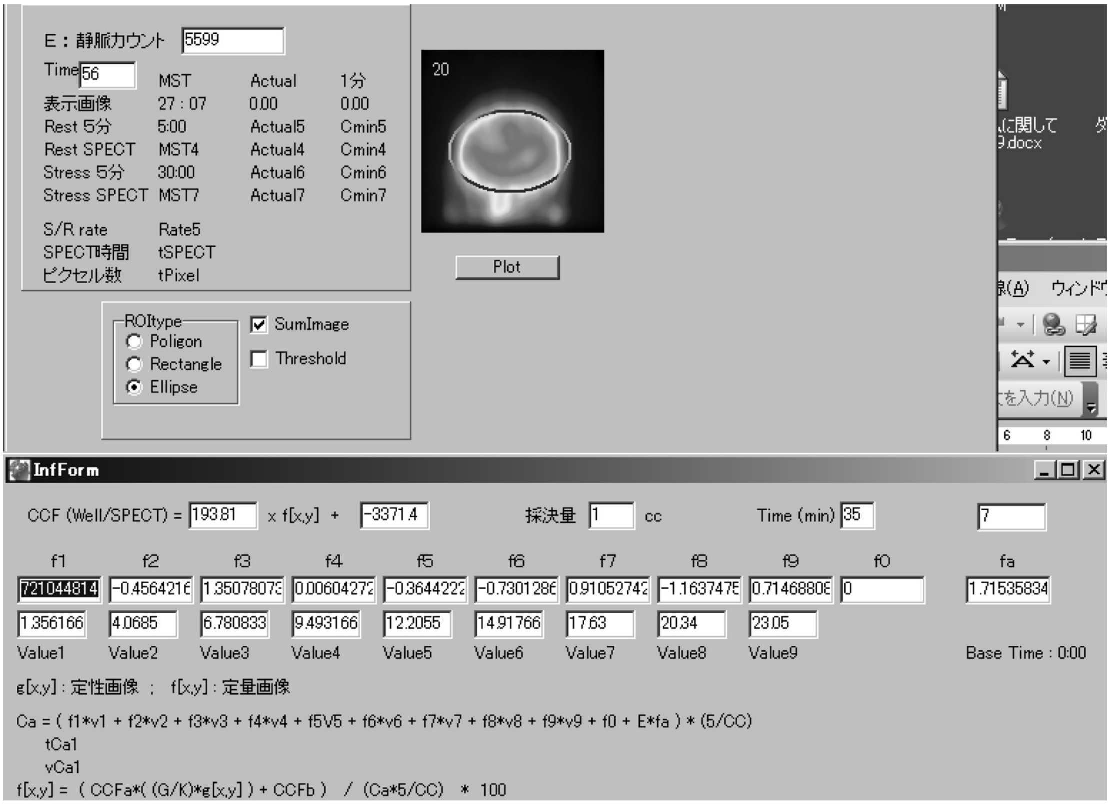



**Fig. 9 You appoint an analysis factor. Designation of CCF by the phantom experiment. CCF appoints the ratio with our experiment. The expression of the multiple regression analysis is appointed beforehand. Other factors have been appointed, too.**

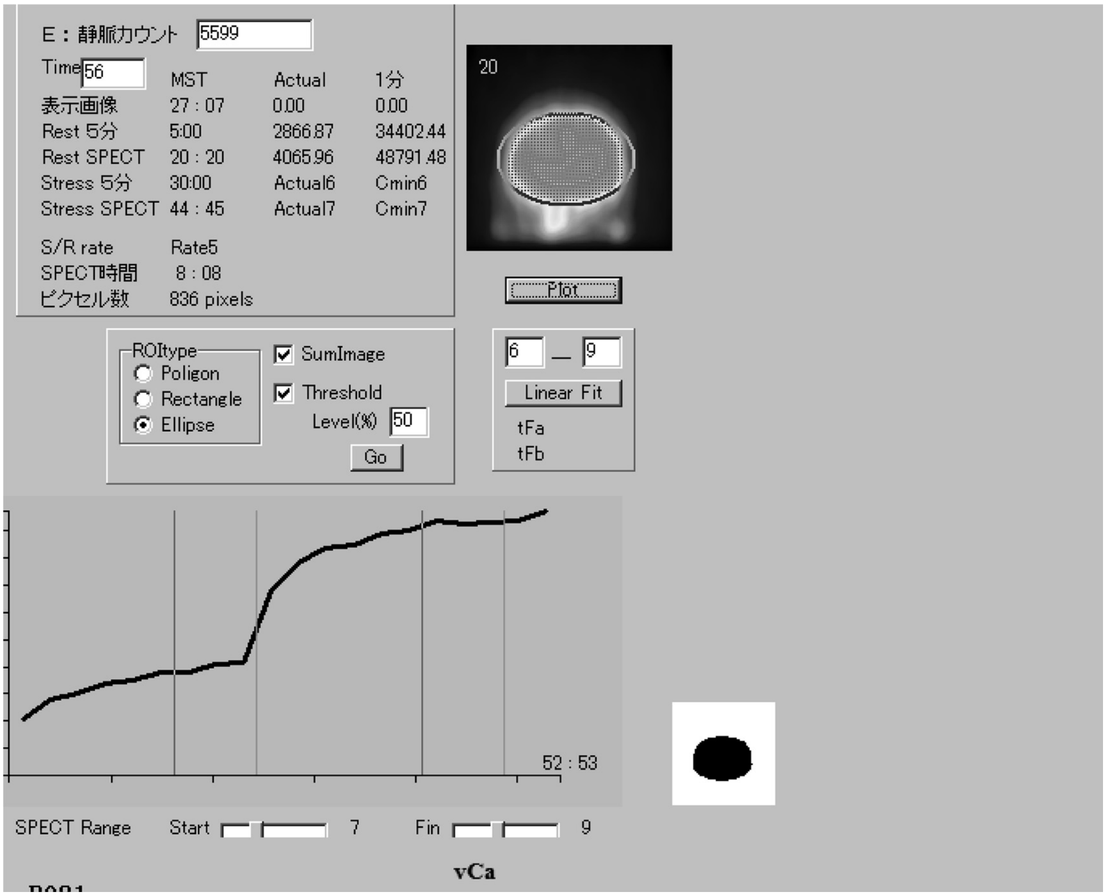



**Fig. 10 You advise it on a condition to list next. Treshhold appoints 50%. You calculate a true load image in Linear-Fit. You appoint a frame to use for a reconfiguration. The red color line starts, and the green line shows an end frame.**

provement of this study (**Fig. 7–13**). You need cross-calibration factor (CCF) calculation to make the derived function that we found in this study use. You find the ratio of your CCF and my CCF beforehand. An SPECT image will be converted into resional cerebral blood flow (rCBF) image by using this software. The rCBF viewer shows an example using 3DSRT (**Fig. 14**).

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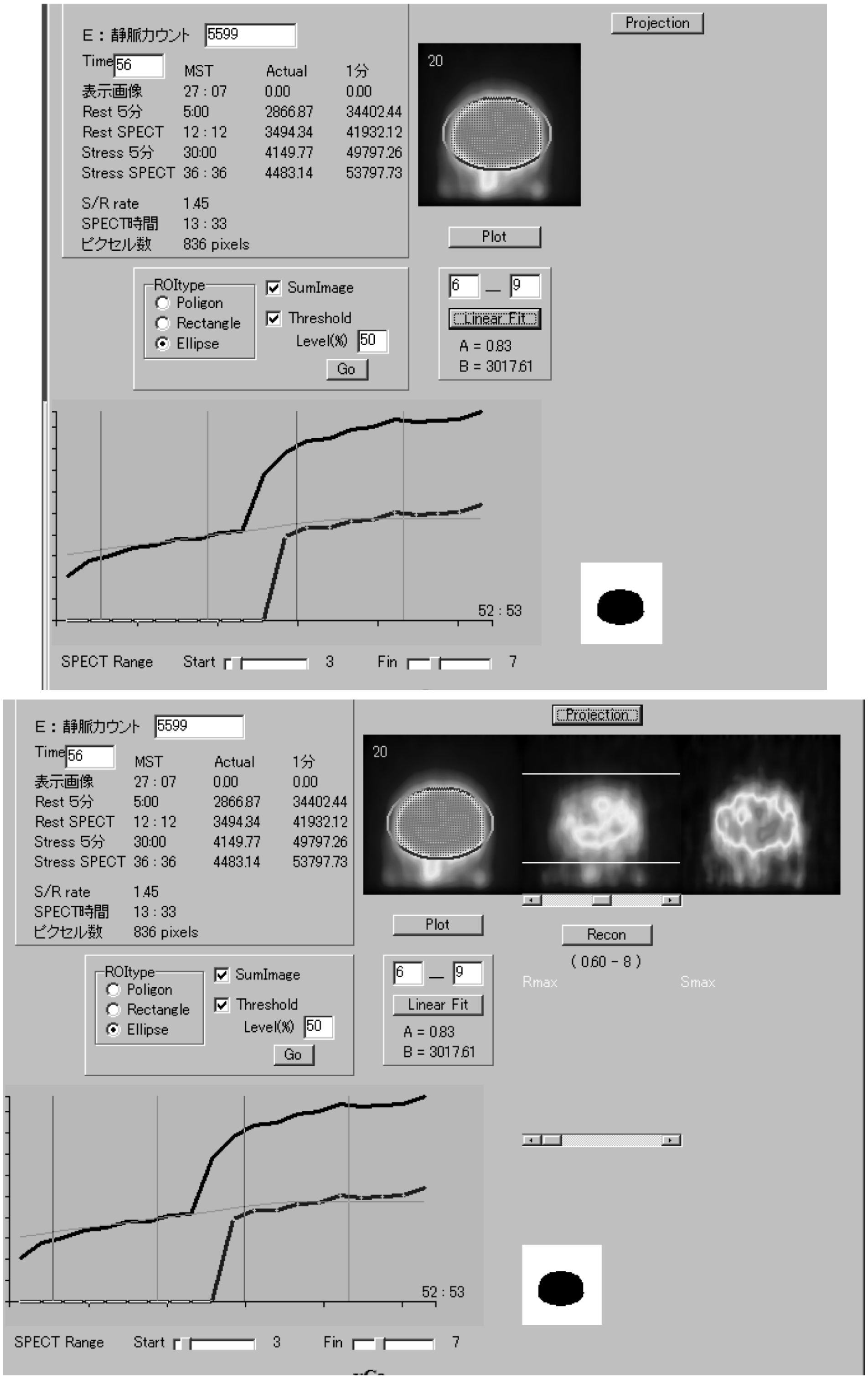


**Fig. 11** Prijection button appears. Reconfiguration GUI appears when You push the button. You appoint the range of the brain image, and it is a brain bottom and designation of the top.

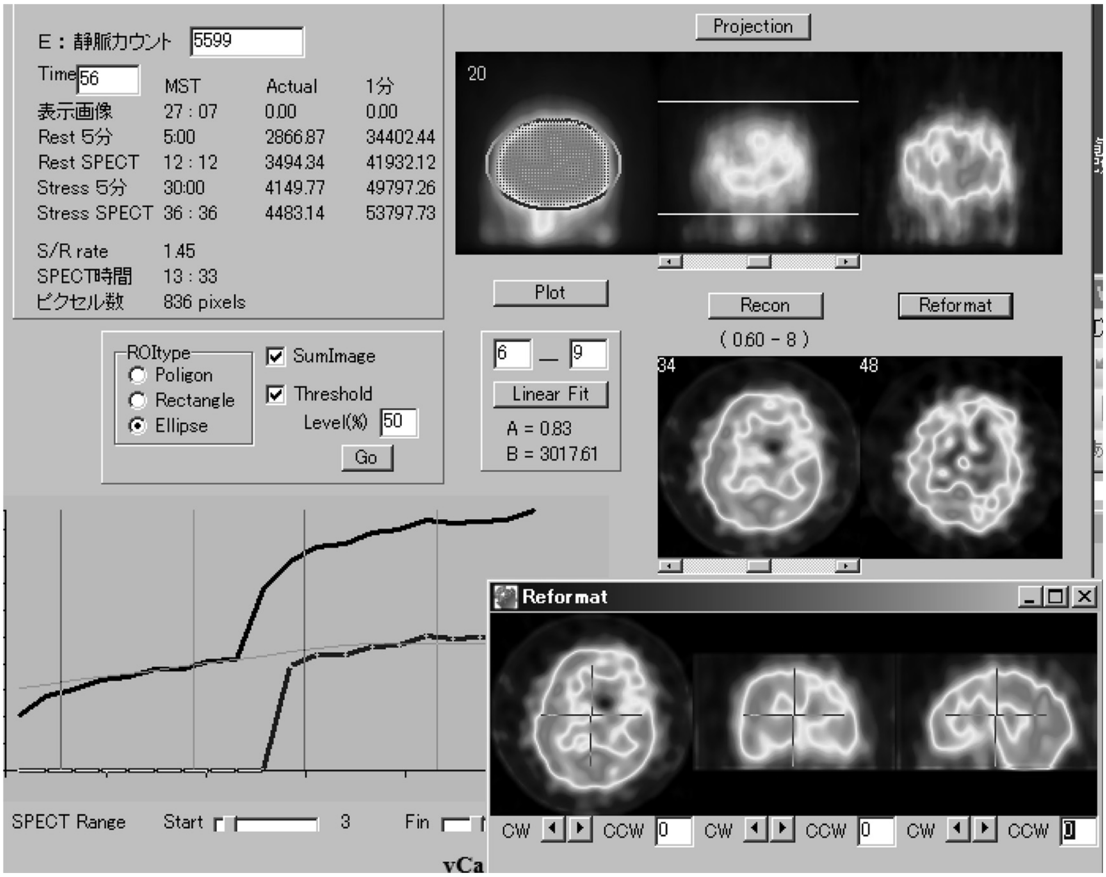


**Fig. 12　The Recon button carries out reconstitution.　You can edit an image axis again when You push the Reformat button.**


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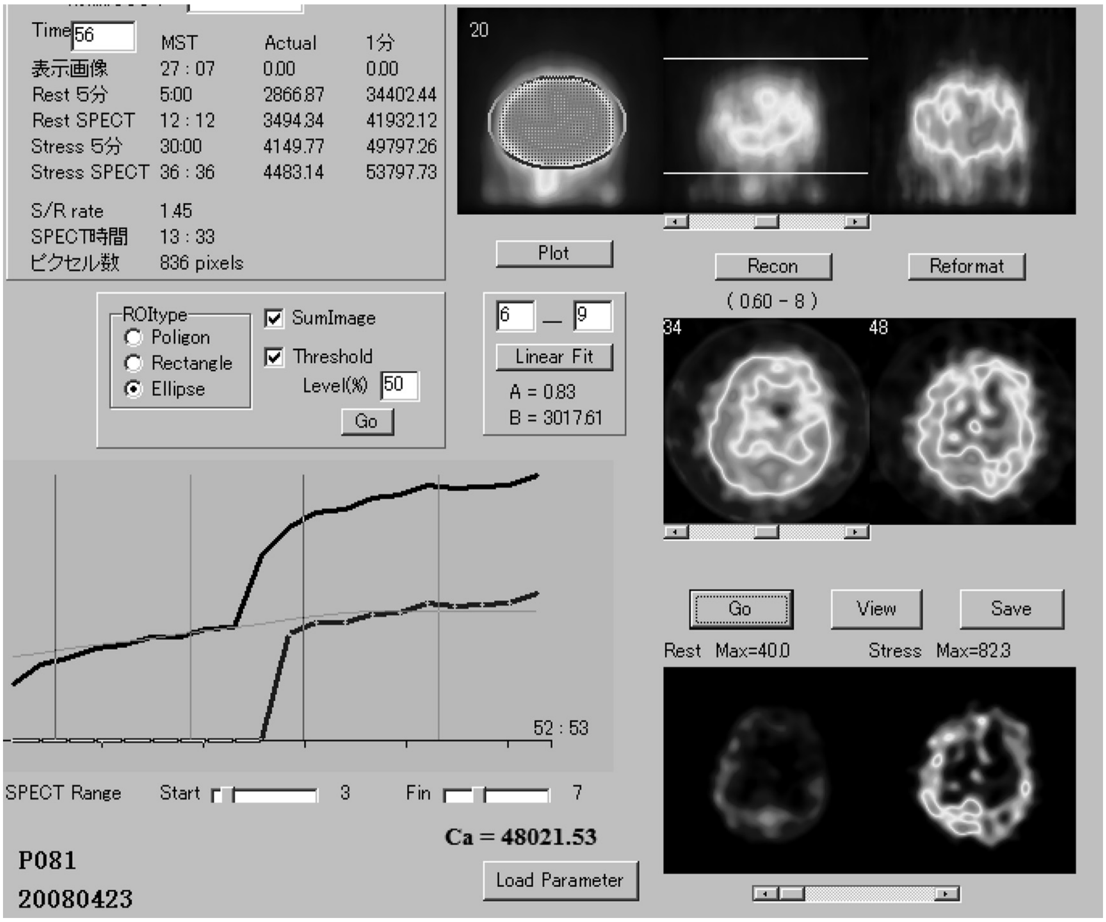


**Fig. 13** **You calculate rCBF with GO button. You confirm rCBF image with View button. You store a result with Save button.**


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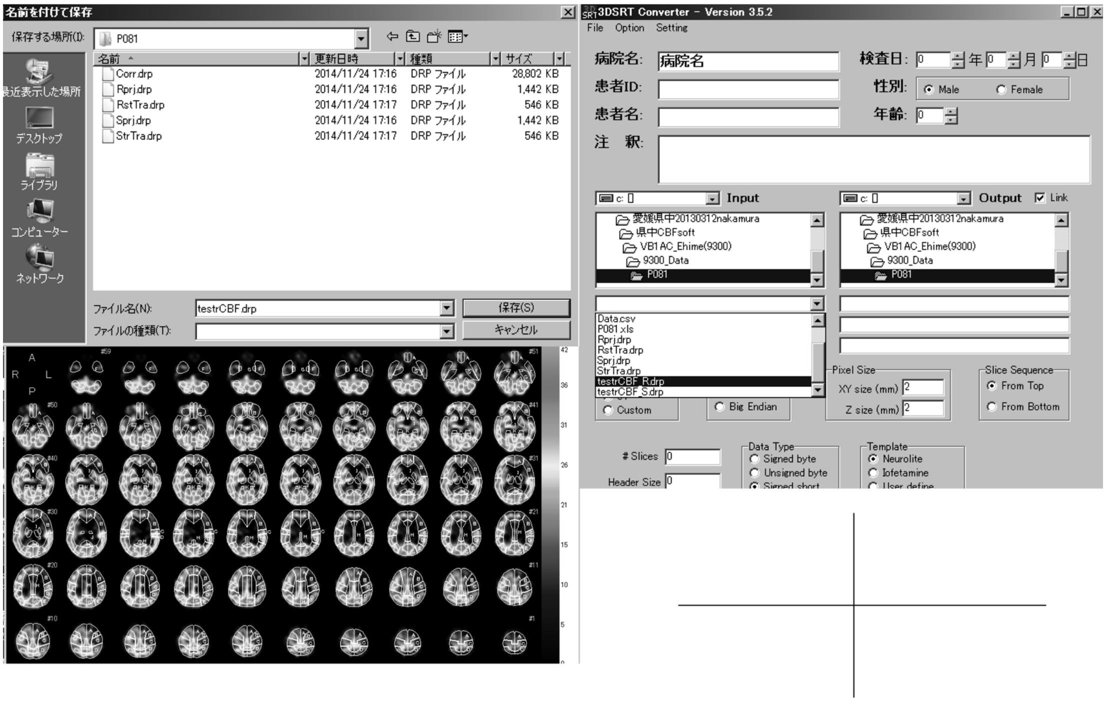


**Fig. 14　The image which You stored is rCBF image.　The indication supports many image software. You read an example using 3DSRT.**

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