



Research Article

# Effect of the Head Reference Angle on the Mean Cerebral Blood Flow during Radionuclide-Angiography with the Patlak Plot Method with Technetium-99m Ethyl Cysteinate Dimer

Hitoshi Hiraki<sup>1,3</sup>, Toshimune Ito<sup>2</sup>, Masahisa Onoguchi<sup>3\*</sup>, Hirotsu Tsuchikame<sup>4</sup>, Masaaki Shishido<sup>3,4</sup>, Takafumi Maeno<sup>4</sup>, Hiroki Sanada<sup>1</sup>, Masao Tago<sup>1,5</sup>

## Abstract

**Background:** The purpose of this study was to clarify the effect of the head reference angle (jaw pull angle) in the cephalocaudal direction on mean cerebral blood flow (mCBF) during radionuclide (RI)-angiography using the Patlak Plot method in CBF Single Photon Emission Computed Tomography (SPECT) testing with <sup>99m</sup>Tc-ECD.

**Methods:** From January 2012 to December 2013, 290 normal patients were retrospectively evaluated with CBF SPECT testing with technetium-99m ethyl cysteinate dimer (<sup>99m</sup>Tc-ECD). The brain Region of Interest (ROI) and mCBF were evaluated during RI-angiography.

**Results:** mCBF of all males and females aged 60–89 years was 40.4 ± 4.2 and 42.2 ± 3.6 (ml/100 g/min), respectively, showing a weak negative correlation with aging. The mCBF was lower in males than in females (p<0.05). The brain ROI size was significantly greater in males with a head reference angle below -10 degrees (p<0.05) and significantly smaller in males with an angle above 5.1 degrees (p<0.05). Brain ROI size was significantly greater in females with a head reference angle below -10 degrees (p<0.05) and significantly smaller for females with an angle above 10 degrees (p<0.05). There was no significant difference in brain ROI sizes between males and females. The mCBF was significantly lower in both genders with head reference angle ±10 degrees (p<0.05).

**Conclusion:** The mCBF was found to be significantly lower when the head reference angle during RI-angiography using the Patlak Plot method and <sup>99m</sup>Tc-ECD was greater than ±10 degrees.

**Keywords:** Technetium-99m ethyl cysteinate dimer, Patlak plot, Region of interest, Mean cerebral blood flow, Head reference angle

**Abbreviations:** BPI: Brain Perfusion Indexes; CBF: Cerebral Blood Flow; CT: Computed Tomography; mCBF: Mean Cerebral Blood Flow; MRI: Magnetic Resonance Imaging; RI: Radionuclide; ROI: Region of Interest; SPECT: Single Photon Emission Computed Tomography

## Introduction

In Japan, the application of Single Photon Emission Computed Tomography (SPECT) for cerebral blood flow changed from mainly inpatients to mainly outpatients due to the spread of the diagnosis procedure combination system. In addition, the indications for SPECT changed from cerebrovascular diseases to degenerative diseases. Furthermore, the population changed due to aging factors such as an increase in the number of people aged 65 years and over, which was the result of the decline in age group-specific mortality rates. Against this background, the number of patients undergoing cerebral perfusion SPECT examinations was elderly and an increasing number of patients had difficulty with the imaging head position due to spinal flexion and other factors.

SPECT provides information on brain function and blood circulation that is difficult to obtain from anatomical images obtained with Computed Tomography

## Affiliation:

<sup>1</sup>Department of Central Radiology, Teikyo University Mizonokuchi Hospital, Kawasaki, Japan

<sup>2</sup>Department of Radiological Technology, Faculty of Medical Technology, Teikyo University, Tokyo, Japan

<sup>3</sup>Department of Quantum Medical Technology, Graduate School of Medical Sciences, Kanazawa University, Kanazawa, Japan

<sup>4</sup>Department of Radiology, Saiseikai Yokohamashi Tobu Hospital, Yokohama, Japan

<sup>5</sup>Department of Radiology, Teikyo University Mizonokuchi Hospital, Kawasaki, Japan

## \*Corresponding author:

Masahisa Onoguchi, Department of Quantum Medical Technology, Graduate School of Medical Sciences, Kanazawa University, Kanazawa, Japan.

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(CT) and Magnetic Resonance Imaging (MRI). SPECT has been shown to be useful in various central nervous system diseases [1-3]. Positron emission tomography using <sup>18</sup>F-fluorodeoxyglucose (<sup>18</sup>F-FDG) is more sensitive than cerebral blood flow SPECT for detecting decreased glucose metabolism, especially in imaging studies carried out to assess dementia, but is not covered by insurance in Japan [4]. The number of cases in which it can be performed is limited in Japan. In addition, compared to <sup>123</sup>I-based cerebral blood flow SPECT agents, <sup>99m</sup>Tc-based cerebral blood flow SPECT agents are more suitable for screening degenerative diseases and require shorter acquisition times. Therefore, SPECT of cerebral blood flow using radiopharmaceuticals such as technetium-99m ethyl cysteinate dimer (<sup>99m</sup>Tc-ECD) [5-8] is used in many facilities because it is known to be useful for differential diagnoses of dementia by assessing areas of reduced blood flow [9,10]. It is important to understand cerebral blood flow dynamics in central nervous system diseases in the elderly using cerebral blood flow SPECT [11,12]. It is especially useful when the entire brain is diffusely hypoperfused [13]. In cerebral blood flow SPECT using <sup>99m</sup>Tc-ECD, the Patlak Plot method, which was developed by Matsuda et al. [14] is widely used because it is noninvasive and simple to use [14-19]. The Patlak Plot method requires radionuclide-angiography (RI-angiography) of the patient's frontal view of the tracer to pass from the heart to the brain immediately after the tracer is administered intravenously for quantitative analysis [14]. From the obtained RI-angiography images, the Regions of Interest (ROIs) were hand-drawn over the bilateral brain hemispheres (ROIbrain) and aortic arch (ROIaorta) [14]. The ROIbrain should be set in the parenchyma of the brain, avoiding the scalp, nasal cavity, and cerebellum [20-21]. In particular, it has been shown that the setting of the ROIbrain has the greatest impact on quantitative analysis [21]. In order to set the ROIbrain only in the parenchyma of the brain, the angle of jaw pull to the cephalocaudal direction of the head during RI-angiography is important, and there is no report that has verified the influence from that angle. The purpose of this study was to clarify the effect of the reference angle of the head during RI-angiography using the Patlak Plot method on mean cerebral blood flow (mCBF) in cerebral blood flow SPECT using <sup>99m</sup>Tc-ECD.

## Materials and Methods

### Patients

Between January 2012 and December 2013, 290 patients who visited an outpatient memory loss clinic and underwent cerebral blood flow SPECT scans and were judged to be normal were included in the study. One cerebral blood flow SPECT study per patient was included. The patients ranged in age from 60 to 89 years, the mean age and standard deviation were 77.8 ± 7.0 years for males and 78.8 ± 6.0 years for females (Table 1). The patients with no apparent abnormality on cerebral blood flow SPECT, no abnormal signal areas on head MRI or head CT performed on the same day as cerebral blood flow SPECT, and the patients who walked independently were included in the study. This study

was approved by the ethical review committee of the institution to which the researcher belongs.

### Equipment and acquisition conditions

A two-detector gamma camera Symbia-E equipped with a low energy high resolution collimator and a workstation GMS-7700R (Cannon Medical Systems Inc.) were used for processing. To prevent increased blood flow in the visual area due to light stimulation, the patient was placed in a supine position on a bed and kept in a resting position with closed eyes [22]. Dynamic acquisition was started 10 minutes later simultaneously with radiopharmaceutical administration. Dynamic acquisition was performed with a detector placed in front of the patient, covering the area from the heart to the brain.

The detector was set so that the detector in front of the patient and the patient's body surface (head to chest) were parallel and at the shortest distance apart. <sup>99m</sup>Tc-ECD was administered into the ulnar cutaneous vein of the right arm using 20 mL saline at a constant flush for 10 seconds and under the constant conditions of at least 15 mL of saline and an infusion rate of 1.5–2.0 mL/sec. This ensured the conditions for a constant rate of infusion of 1.0–1.5 mL/sec or more [23]. The angle of the right arm during administration was raised to a right angle (approximately 90 degrees) between the arm and the body to improve bolus usability (Figure 1) [20,23]. One frame per second was acquired for 120

Table 1: Age stratified participants.

Age-group	Male			Female		
	Number	Mean	SD	Number	Mean	SD
60–69 years	15	65.3	2.9	13	65.5	2.3
70–79 years	45	75.3	2.8	74	75.3	2.6
80–89 years	49	84	2.7	94	83.5	2.7
All	109	77.8	7	181	78.8	6



Figure 1: Right upper extremity positioning during radiopharmaceutical administration.

seconds with a  $128 \times 128$  matrix immediately after administration, and the magnification ratio was set to 1.0 [24]. If it was difficult to secure a vessel in the ulnar cutaneous vein of the right arm, the elbow median vein and radial cutaneous vein of the right arm were selected, in that order, and only three vessels were included. After the dynamic acquisition was completed, the indwelling needle was removed and planar images of both sides of the head were acquired using a  $512 \times 512$  matrix,  $2.67\times$  magnification, and one minute acquisition time to measure the angle of the head during dynamic acquisition (Figure 2). SPECT acquisition was started 5 minutes after administration. SPECT acquisition was performed using a  $128 \times 128$  matrix,  $2.29\times$  magnification (pixel size 2.1 mm), 90 projections ( $4^\circ/\text{step}$ , continuous), six sets of 3 minutes per frame, 18 minutes of acquisition time, and a 13.5 cm rotation radius [25]. The filtered back projection method was used for image reconstruction, and a Butterworth filter (cutoff frequency 0.60 cycles/cm, order 8) was used as a preprocessing filter. The attenuation was corrected using the Chang method (attenuation coefficient of  $0.09 \text{ cm}^{-1}$ , and a uniform attenuation map was created with a background threshold of 7%. The photopeak window for  $^{99m}\text{Tc}$  was set as a 15% energy window centered at 141 keV. The mCBF was calculated using the Patlak Plot method, which was similar to the method reported by Matsuda et al. [15,16]. The ROIbrain and ROIAorta were hand-drawn [14] for Patlak Plot measurements and the ratio of the ROIbrain size to the ROIAorta size was 10:1 (Figure 3) [14]. A ROIbrain was set on each side to avoid the scalp and nasal cavity and did not extend beyond the cerebral hemispheres. The ROIAorta was set so that it did not extend beyond the aortic arch and did not overlap with the venous or pulmonary circulatory phases. The Brain Perfusion Indexes (BPIs) of the left and right cerebral hemispheres were calculated from the time activity curves obtained from the ROIbrain and ROIAorta, respectively, using the Patlak Plot method and the obtained BPI was converted to the mCBF using the relationship formula between BPI and mCBF reported in a previous study by Matsuda et al. [16]. This equation used the early picture method as the conversion equation to  $^{133}\text{Xe}$ . The equation is shown below.



Figure 2: Positioning during head bilateral image acquisition.

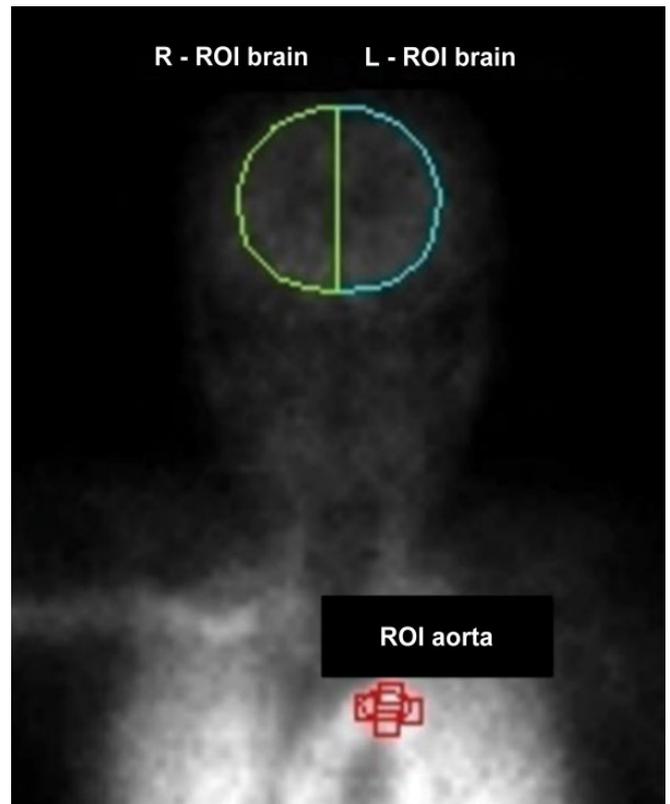


Figure 3: Regions of Interest (ROIs) drawn over the aortic arch and the bilateral brain hemispheres in sequential images of radionuclide angiography using Technetium-99m Ethyl Cysteinate Dimer ( $^{99m}\text{Tc}$ -ECD).

$$\text{mCBF} = 2.60 \times \text{BPI} + 19.8 \quad (1)$$

The ROIbrain and ROIAorta sizes were recorded when the mCBF was calculated. Lassen's correction ( $\alpha$  value: 2.59) [26,27] was applied to the quantitative images using the report by Kawahata et al. [28]. A board-certified nuclear medicine technologist with more than 20 years of experience in nuclear medicine performed the entire process, and the entire series of actions from image processing to quantitative analysis was performed by one person.

### Head reference angle measurements

The bilateral planar images of the head taken after the end of the dynamic acquisition period were used to measure the jaw pull angle in the head-caudal direction during the dynamic acquisition (Figure 4). The jaw pull angle of the head in the cephalocaudal direction was measured using a straight line connecting the frontal and occipital poles of the cerebrum as the reference line, and the average of the two angles was used. The reference angle range was defined as  $\pm 5.0$  degrees around the reference angle. Angles were classified as  $-10.0$  degrees or less,  $-9.9$  to  $-5.1$  degrees, and  $-5.0$  to  $5.0$  degrees (reference angle),  $5.1$  to  $9.9$  degrees, and  $10.0$  degrees or more.

### Radiopharmaceutical

The  $^{99m}\text{Tc}$ -ECD syringe formulation 600 MBq (FUJIFILM

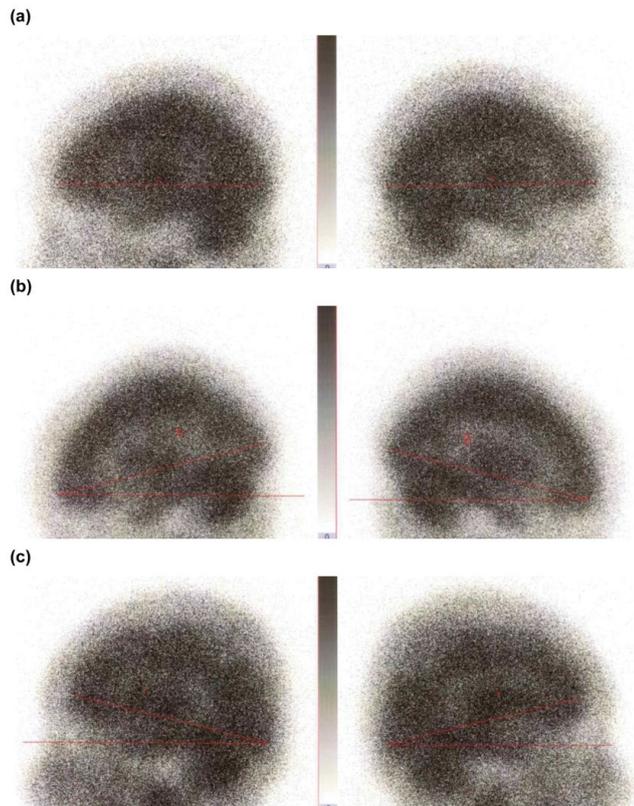
Toyama Chemical Co., Ltd.) was administered as a full dose. Doses ranged from 600 to 900 MBq.

**Statistical analysis**

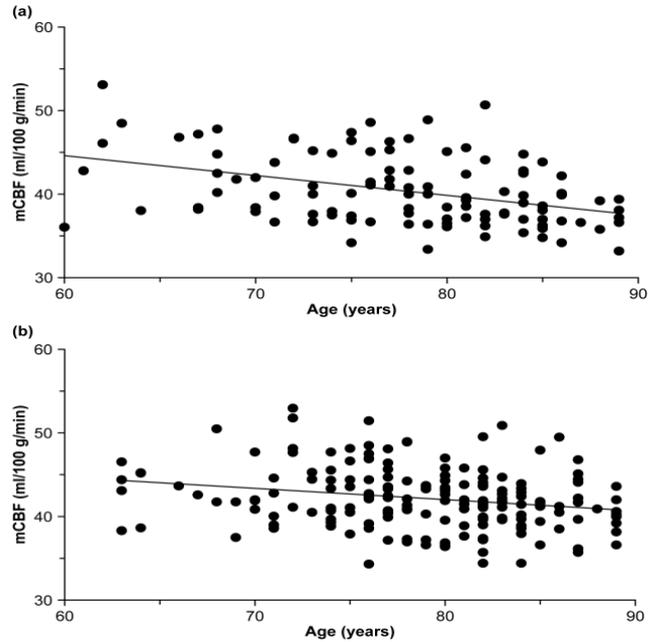
Statistical processing was performed using Graphpad Prism 9. The mean between the two groups was tested for significant differences using an unpaired t test. The Kruskal–Wallis and Dunnet-type multiple testing methods were used to test for significant differences between groups at each angle. A P value less than 0.05 was considered statistically significant.

**The ROIbrain relationship for different reference angles**

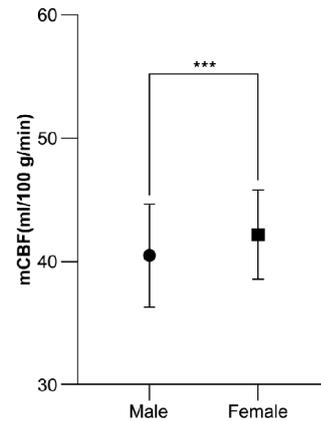
Table 3 and Figure 7 show the ROIbrain number of pixels by gender and reference angle classification of the subjects. The overall mean for males was  $177.0 \pm 17.9$  and it was  $197.3 \pm 10.9$  for  $-10.0$  degrees and below,  $184.9 \pm 15.3$  for  $-9.9$  to  $-5.1$  degrees,  $178.3 \pm 17.3$  for  $-5.0$  to  $5.0$  degrees,  $165.6 \pm 13.3$  for  $5.1$  to  $9.9$  degrees, and  $162.6 \pm 11.1$  for  $10.0$  degrees and above. Compared to the reference angle of  $-5.0$  to  $5.0$  degrees, the values below  $-10.0$  degrees were predominantly higher ( $p < 0.05$ ), while the values between  $5.1$  and  $9.9$  and above  $10.0$  were significantly lower ( $p < 0.05$ ). There was no significant difference between  $-9.9$  and  $-5.1$ . The overall mean for females was  $172.8 \pm 20.1$  and it was  $193.0 \pm 17.5$  for  $-10.0$  degrees and below,  $171.7 \pm 12.8$  for  $-9.9$  to  $-5.1$  degrees,  $169.8 \pm 15.0$  for  $-5.0$  to  $5.0$  degrees,  $158.5 \pm 11.2$  for  $5.1$  to  $9.9$  degrees, and  $142.7 \pm 10.3$  for  $10.0$  degrees or above.



**Figure 4:** Bilateral images of the head for measurement of the head-jaw pull angle (a)  $\pm 0$  degrees (reference angle); (b) Jaw outward (-direction); (c) Jaw backward (+direction).



**Figure 5:** Relationship between age and mean cerebral blood flow (mCBF) by sex (a) Male; (b) Female.



**Figure 6:** Comparison of male and female mCBF

Compared to the reference angle of  $-5.0$  to  $5.0$  degrees, the values below  $-10.0$  degrees were predominantly higher ( $p < 0.05$ ) and those above  $10.0$  degrees were predominantly lower ( $p < 0.05$ ). There was no significant difference between  $-9.9$  to  $-5.1$  and  $5.1$  to  $9.9$  degrees. There was no significant difference in the overall mean ROIbrain between males and females (Figure 8).

**Relationship between the mCBF at different reference angles**

Table 4 and Figure 9 show mCBF (ml/100g/min) by gender and reference angle classification, respectively. The overall mean for males was  $40.4 \pm 4.2$  and it was  $37.3 \pm 1.4$  for  $-10.1$  degrees and below,  $40.5 \pm 3.4$  for  $-10.0$  to  $-5.1$  degrees,  $41.5 \pm 4.3$  for  $-5.0$  to  $5.0$  degrees,  $40.0 \pm 4.8$  for  $5.1$  to  $10.0$  degrees, and  $37.9 \pm 2.0$  for  $10.1$  degrees and above. Compared to the reference angle of  $-5.0$  to  $5.0$  degrees, the values below  $-10.1$  degrees and above

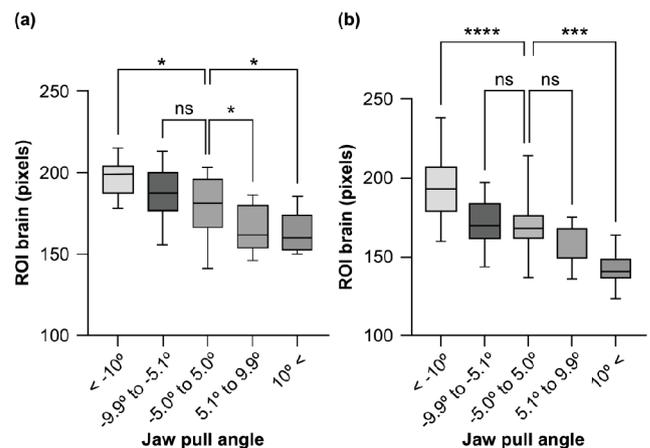
10.1 degree were significantly lower ( $p < 0.05$ ). There was no significant difference between  $-10.0$  to  $-5.1$  degrees and  $5.1$  to  $10.0$  degrees. The overall mean for females was  $42.2 \pm 3.6$  and it was  $41.2 \pm 3.1$  for  $-10.1$  degrees and below,  $42.8 \pm 3.5$  for  $-10.0$  to  $-5.1$  degrees,  $42.9 \pm 3.8$  for  $-5.0$  to  $5.0$  degrees,  $42.5 \pm 3.6$  for  $5.1$  to  $10.0$  degrees, and  $39.5 \pm 2.5$  for  $10.1$  degrees and above. Compared to the reference angle of  $-5.0$  to  $5.0$  degrees, the values below  $-10.1$  degrees were predominantly low ( $p < 0.05$ ) and above  $10.1$  degrees were significantly low ( $p < 0.05$ ). There was no significant difference between  $-10.0$  to  $-5.1$  degrees and  $5.1$  to  $10.0$  degrees.

## Discussion

In this study, we evaluated the effect of the reference angle of the head in the cephalocaudal direction (jaw pull angle) during RI-angiography to measure the mCBF in a quantitative analysis of cerebral blood flow using the Patlak Plot method with  $^{99m}\text{Tc}$ -ECD (Figure 4). Otake et al. [21] reported that the inclusion or exclusion of the cerebellum and nasal cavity in the ROIbrain is a major factor and that this has the greatest impact on quantitative analyses [21]. The ROIbrain size was verified based on the reference angle of the head in the cephalocaudal direction during RI-angiography and its effect on mCBF was verified. First, the relationship between age and gender of the subjects and mCBF was verified and compared with previous studies (Table 2; Figures 5 and 6). The results showed that there was a significant difference in the mCBF between males and females. We therefore evaluated the mCBF of males and females separately. Next, we examined the relationship between the reference angle and ROIbrain size by gender and found that when the reference angle was greater than  $\pm 10$  degrees, the ROIbrain size was likely to be over- or under-set for both genders (Table 3; Figures 7 and 8). Next, the relationship between the reference angle and the mCBF by gender was examined and it was shown that the mCBF may be underestimated when the ROIbrain size was overestimated or underestimated (Table 4; Figure 9).

The relationship between age and sex of the patients and mCBF was negative and weak, with a mCBF of  $-0.40$  for males aged 60 to 89 years. Similarly, females showed a negative and weak correlation of  $-0.22$  (Table 2). This was in agreement a report by Tanaka et al. [29] that suggested mCBF had a significant negative correlation with aging [29-30]. Next, a comparison of mCBF between males and females showed that males predominantly had a lower mCBF than females. This is consistent with the results of the present study, in which Takeda et al. [31] reported that cerebral blood flow in males was lower than that in females [31]. In a study by Matsuda et al. [15] in which the Patlak Plot method with  $^{99m}\text{Tc}$ -HMPAO was used, mCBF was reported to be  $44.9 \pm 2.2$  ml/100g/min on average in 60- to 76-year-olds, and the present results were similar to these values. Therefore, we believe that the subject of our study is appropriate.

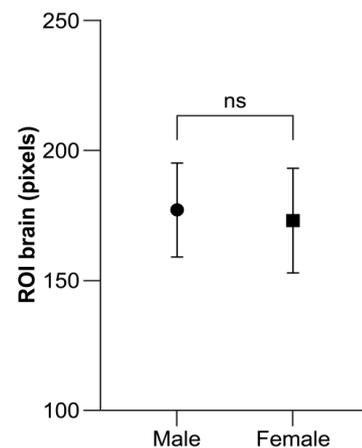
In terms of the relationship between the ROIbrain sizes for different reference angles, first, the mean ROIbrain size for males was larger than the mean ROIbrain size for females with respect



**Figure 7:** Relationship between brain ROI and head reference angle by gender (a) Male; (b) Female.

**Table 2:** Relationship between age and mean cerebral blood flow (mCBF) by gender and age group.

Age-group	Male			Female		
	mCBF	SD	Correlation	mCBF	SD	Correlation
60–69 years	43.5	4.6	-0.40	43	3.5	-0.22
70–79 years	41.1	4		42.9	3.9	
80–89 years	38.8	3.4		41.5	3.2	
All	40.4	4.2		42.2	3.6	
mCBF (ml/100 g/min)						



**Figure 8:** Comparison of male and female brain ROI.

to the size of the ROIbrain for each gender (Table 3). Allen et al. reported that males had larger brain volumes than females [32], and their results were similar to those of Allen et al. However, the images were obtained from a system with a resolution of approximately 10%, and no significant difference was found due to the blurring of nuclear medicine images caused by pixel size and low counts (Figure 7). Next, for the male ROIbrain size, values below  $-10.0$  degrees were significantly higher than the reference

ROIbrain, while values between 5.1 and 9.9 degrees and above 10.0 were significantly lower than the reference ROIbrain (Figure 6) The ROIbrain size of the male subject was significantly higher than -10.0 degrees because the ROIbrain size was set widely because the ROIbrain was set using image acquisition from the front of the head, with the cerebral hemispheres collapsed toward the feet, as shown in Figure 4(b). In addition, as can be seen from Figure 4(c), the ROIbrain size from the frontal image was influenced by the ROIbrain from the front view, and the occipital region could not be included in the ROIbrain image, resulting in an underestimation of the ROIbrain and a significantly low value for the ROIbrain size. In a report by Yano et al. [24] the definition was based on the assumption that the jaw was not extremely raised or lowered, and an extremely strong reference angle was shown to affect the ROIbrain, which was consistent with their results. Next, for the female ROIbrain size, the reason was considered to be the same as that for the male ROIbrain size, but because the female ROIbrain size was smaller than the male ROIbrain size, there was a significant difference only between the values below -10.0 degrees and above 10.0 degrees.

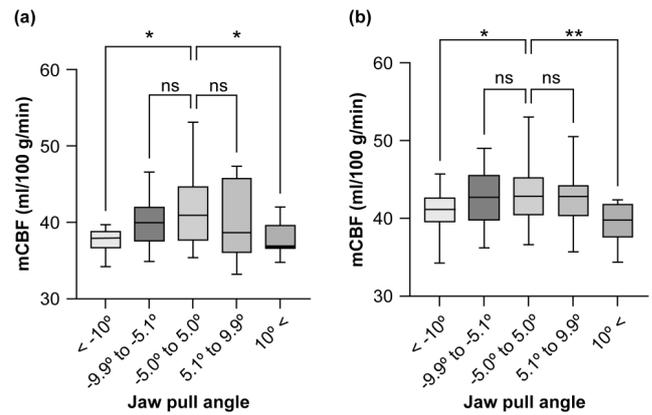
The relationship between the reference angle and mCBF showed that mCBF was significantly lower below -10.0 degrees and above 10.0 degrees in both males and females (Figure 8). The ROIbrain size was significantly larger when the reference angle value was less than -10.0 degrees, suggesting that the ROIbrain size included regions other than the cerebral hemispheres and included the cerebellum. This reduced the counts/pixels included in the ROIbrain measurements, resulting in a significantly lower mCBF value. Similarly, the ROIbrain size was significantly smaller at values of 10.0 degrees or greater. This is because one of the characteristics of <sup>99m</sup>Tc-ECD brain distribution is overestimation of occipital lobe blood flow [33], and when the ROIbrain exceeds 10.0 degrees, there is a high possibility that the occipital lobe is

**Table 3:** Relationship between head reference angle and brain Region of Interest (ROI) by gender.

Angle	Male		Female	
	ROI brain	SD	ROI brain	SD
<-10°	197.3	11	193	18
-9.9° to -5.1°	184.9	15	171.7	13
-5.0° to 5.0°	178.3	17	169.8	15
5.1° to 9.9°	165.6	13	158.5	11
10°<	162.6	11	142.7	10
All	177	18	172.8	20

**Table 4:** Relationship between head reference angle and mCBF by gender.

Angle	Male		Female	
	mCBF	SD	mCBF	SD
<-10°	37.3	1.4	41.2	3.1
-9.9° to -5.1°	40.5	3.4	42.8	3.5
-5.0° to 5.0°	41.5	4.3	42.9	3.8
5.1° to 9.9°	40	4.8	42.5	3.6
10°<	37.9	2	39.5	2.5
All	40.4	4.2	42.2	3.6



**Figure 9:** Relationship between head reference angle and mCBF by gender (a) Male; (b) Female.

**Table 5:** Relative error of mCBF by reference angle.

Angle	Male	Female
	mCBF	mCBF
<-10°	-10.0%	-4.0%
10°<	-8.6%	-7.9%

**Table 6:** Correction coefficient of mCBF by reference angle.

Angle	Male	Female
	mCBF	mCBF
<-10°	×1.11	×1.04
10°<	×1.09	×1.09

not included. Therefore, the number of counts/pixels included in the ROIbrain was reduced and mCBF was considered to be significantly lower.

Miyazaki et al. [34] reported that the relationship between ROI and mCBF showed that as the counts/pixel in the ROIbrain increased, mCBF also increased proportionally, which is consistent with their results.

These results are consistent with the report by Yano et al. [24] which showed that an extremely strong jaw pull angle, such as an extremely raised or lowered jaw during RI-angiography, affects the ROIbrain size when mCBF is obtained using the Patlak Plot method and <sup>99m</sup>Tc-ECD [33]. In the present validation, it was inferred that mCBF is significantly lower when the jaw is extremely lowered below -10.0 degrees and when the jaw is extremely raised above 10.0 degrees, due to the effect of the size of the ROIbrain.

Based on the results of this verification, the effect on mCBF at reference angles greater than ±10 degrees is shown in Table 5 as a relative error. It was clear that mCBF was significantly lower when the reference angle was ±10 degrees. Therefore, when dynamic acquisition was performed at a reference angle of ±10 degrees or higher, the mCBF can be converted to the mCBF at the reference angle by using the correction coefficient shown in Table 6.

This study has several limitations. First, the Patlak Plot method requires many manual operations, and since the data differs from patient to patient, it has been reported that the results may vary

depending on the surgeon's experience level and processing standards [21], and it is necessary to verify this series of processes with many surgeons. If interoperator variability is minimized, the accuracy may be further improved. Second, mCBF has been reported to decrease with age [17]. The present study was conducted with elderly subjects aged 60 to 89 years (mean age: approximately 80 years). Continuous follow-up of the subjects may improve the accuracy of the normality judgment and the accuracy of determining that the cause of the decrease in mCBF was due to the size of the ROIbrain. Further validation with a larger number of subjects may improve the accuracy, especially with respect to the collection of reference angles at  $\pm 10.0$  or higher. Finally, because RI-angiography records data from the anterior aspect, it has been reported that the BPI is significantly lower in cases where the ischemic area is deep or occipital [34], and another method should be selected if these are known in advance.

## Conclusions

In order to obtain mCBF using the Patlak Plot method with  $^{99m}\text{Tc}$ -ECD, we measured the reference angle of the head during RI-angiography and verified the effect on ROIbrain sizes and the effect on mCBF. Our results suggested that the reference angle of the head  $\pm 10$  degrees or less during RI-angiography may reduce the effect on mCBF.

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## Conflict of interest

The authors have no relevant conflicts of interest to disclose.

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