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Title

Reproducibility between brain uptake ratio method using anatomic standardization (BUR-AS) and patlak plot method

Short running title

Reproducibility of BUR-AS method

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Abstract

Purpose Patlak plot and brain uptake ratio (BUR) methods have some problems about reproducibility. We formulated BUR method using anatomic standardization (BUR-AS) in statistical parametric mapping algorithm to improve reproducibility. The objective of this study was to demonstrate inter- and intra- operator reproducibility of mean cerebral blood flow (mCBF) using BUR-AS in comparison to conventional BUR (C-BUR) and patlak plot methods.

Methods Images in thirty patients who underwent brain perfusion single photon emission computed tomography (SPECT) studies were retrospectively used in this study. The SPECT images were reconstructed by ordered subset expectation maximization method, which were processed using automatic quantitative analysis for cerebral blood flow of ECD tool. The mean SPECT was calculated from basal ganglia slices of normal side (slice No., 31-40) for a 3-dimensional stereotaxic regional of interest template drew axis images after anatomic standardization. The mCBF was calculated from the mSPECT. Evaluation of reproducibility used the coefficient of variation (CV) and Bland-Altman plot.

Results Both inter- and intra- operator reproducibility, BUR-AS method has lowest the CV and smallest error range about Bland-Altman plot. Then, BUR-AS method mCBF had highest reproducibility of other method.

Conclusion We were demonstrated that BUR-AS method can provide a stable cerebral blood flow to have high inter- and intra- operator reproducibility, compared to patlak plot and C-BUR methods.

Key wards

Brain perfusion SPECT, patlak plot method, brain uptake ratio, reproducibility, cerebral blood flow (CBF)

Introduction

Cerebral blood flow (CBF) measurement have reported Xe- computed tomography (CT), perfusion CT using contrast agents, arterial spin labeling method in magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT) and positron emission tomography (PET) (*1-3*). Xe-CT and perfusion CT methods aren't common examinations, because perfusion CT is an invasive method using the contrast agents, and Xe-CT installs only in few institutions. MRI method requires high magnetic field and proprietary software. It isn't a general examination yet. On the other hand, nuclear medicine examinations have been widely performed in quantitative measurement of CBF by SPECT study using ^{99m}Tc-hexamethylpropylene amine oxime (^{99m}Tc-HMPAO), ^{99m}Tc-L,L-ethyl cysteinate dimmer (^{99m}Tc-ECD) and N-isopropyl-p iodoamphetamine (^{123}I-IMP), and PET using ^{15}O-labeling agents. Quantitative measurement of PET study using ^{15}O-labeling agents has higher accuracy than that of SPECT study. However it has some problems that PET study can't perform without cyclotron and synthesis device. In addition, quantitative measurement of SPECT study using ^{123}I-IMP has higher accuracy than other SPECT agents, however a procedure is difficult so that it requires artery blood sampling. However, quantitative analysis using ^{99m}Tc-labeling agents can measure non-invasive without artery blood sampling.

As quantitative analysis of CBF using ^{99m}Tc-ECD, patlak plot method and brain uptake ratio (BUR) has been reported (*4-10*). Patlak plot method is performed in quantitative analysis to calculate mean CBF (mCBF) and regional CBF (rCBF) using SPECT data and radionuclide angiography ranges from vertex to aortic arch part. In addition, BUR method is performed in quantitative analysis to calculate mCBF and rCBF using SPECT data and thorax dynamic data. Where, the mCBF is CBF calculated from dynamic data before Lassen's process, and the rCBF is CBF calculated from SPECT data after Lassen's process using mCBF (*4-6,10*).

It has reported that patlak plot method has mCBF and rCBF variations due to the difference of intra- and inter- operator reproducibility in analysis processing such as following (e.g. drawing the region of interest (ROI) setting of aortic arch and brain, determination of brain perfusion index (BPI), axis setting of SPECT image reconstruction, slices selection and ROI setting of normal basal ganglia, etc.), in addition those improvements have been proposed (*4,10-14*).

It has also reported that BUR method has mCBF and rCBF variations due to the difference of intra- and inter- operator reproducibility in analysis processing such as following (e.g.

drawing the region of interest (ROI) setting of aortic arch, gamma function fitting process of time activity curve (TAC), axis setting of SPECT image reconstruction, slices selection and ROI setting of normal basal ganglia, etc.), in addition those improvements have been proposed (*4,10-11,15-17*). These quantitative analysis errors may be decreased diagnostic accuracy about follow-up and determination of treatment adaptation. Therefore, reproducibility of CBF is important to maintain diagnostic accuracy.

Takaki et al. have reported that rCBF reproducibility was improved with use of SPECT images which were anatomic standardization in statistical parametric mapping (SPM) algorithm to automate slice selection ranges and ROI setting of basal ganglia in Lassen's process (*12)*. However, this method using anatomic standardization hasn't been applied to mean SPECT (mSPECT) necessary to calculate the mCBF about BUR method. We was defined BUR with anatomic standardization in SPM algorithm (BUR-AS) method that analyzed mSPECT using this method. BUR-AS method is expected to improve inter- and intra- operator reproducibility about mCBF. The objective of this study was to demonstrate inter- and intra- operator reproducibility of mCBF using BUR-AS method in comparison to conventional BUR (C-BUR) and patlak plot methods.

Material and Methods

Subjects

Images in thirty patients (11 men and 19 women, age range 25–88 years, mean age 71 years) who underwent brain perfusion SPECT studies using ^{99m}Tc-ECD in 2013 were retrospectively used in this study. These subjects had clinical information as following; one encephalosis, six Parkinson disease, two moyamoya disease, three degeneration disease, four Alzheimer's disease, two dementia with Lewy Bodies, one frontotemporal dementia, two internal carotid artery (ICA) stenosis, three ICA occlusion, four dementia, cerebral infarction and one normal case. Permission for this study was obtained from the hospital ethics committee.

Acquisition protocols

^{99m}Tc-ECD imaging was performed using a dual-headed SPECT scanner (Infinia3, GE Healthcare Co., Ltd., Tokyo, Japan). Radionuclide angiography ranges from vertex to aortic arch part for 2min (1s/frame, 128×128 matrix, zoom factor 1.0, pixel size 4.42mm) was obtained using 1 of the 2 detectors equipped with a low-energy high-resolution parallel-holl collimators and a 140 keV ± 10% energy window after a bolus injection of 600 MBq of

^{99m}Tc-ECD into the right brachial vein. The SPECT study was performed using the same collimators and energy window. A projection data was acquired 64×64 matrix (zoom factor 2.0, pixel size 4.42mm) and continuous over 360 degrees in 4 degrees steps for 5 rotations at 4 min per rotation.

Patlak plot method processing

Patlak plot method was performed manual processing by Xeleris ver.3.0 (General Electric Healthcare Co., Ltd., Tokyo, Japan). Using radionuclide angiography data which included aortic arch part from vertex, manual ROIs were drawn over the aortic arch and bilateral brain hemispheres in sequential images of radionuclide angiography and made TAC. Then we determined BPI and calculated mCBF using regression Equation 1 based on the ^{133}Xe method (*18,19*).

$$\mathrm{mCBF} = 2.59 \cdot \mathrm{BPI} + 19.8 \qquad (1)$$

BUR method processing

C-BUR method was performed manual processing by Xeleris ver.3.0. TAC to calculate an area under curve (AUC) was obtained by manual ROI setting on the aortic arch using radionuclide angiography. A location of aorta ROI was manually determined. TAC was fitted with the gamma function, and the AUC was calculated. The AUC divided by ROI area, and was converted counts per square centimeter. SPECT images reconstructed by manual axis setting using ordered subset expectation maximization (OSEM) method. Reconstruction parameters were subsets of 6, iterations of 8 and Butterworth filter (order 8, cut-off frequency 0.49 cycle/cm). An attenuation correction performed using Chang method (attenuation coefficient 0.09cm^{-1}, threshold 13%) (*20*), however scatter correction didn't performed. Slice selections of basal ganglia determined from transverse images of manual axis setting, and ROIs to calculate the mSPECT drew manual on normal side, which was calculated using Equation 2.

$$\text{mSPECT}=\frac{\text{SPECT counts in ROI of normal basal ganglia side (counts)}}{\text{ROI area (pixel)}} \qquad (2)$$

BUR-AS method was performed manual and automatic processing by Xeleris ver.3.0 and personal computer. The AUC converted counts per square centimeter, which used same processing as C-BUR method.

The SPECT images were reconstructed by OSEM method, which were automatically processed using automatic quantitative analysis for cerebral blood flow of ECD tool (AQCEL: Fujifilm RI pharma Co., Ltd. Tokyo, Japan) (*12-13,21*). Image reconstruction and attenuation correction parameters used same processing as C-BUR method, and scatter correction didn't also performed. Slice ranges of basal ganglia selected No.31-40 slices of transversal images after anatomic standardization as shown in Figure 1 (*12*). The ROIs were automatically set on standardized image slice using a 3-dimensional stereotaxic ROI template (3DSRT: Fujifilm RI pharma Co., Ltd. Tokyo, Japan). The ROIs composed of 12 segments (callosomarginal, precentral, central, parietal, angular, temporal, posterior cerebral, pericallosal, lenticular nucleus, thalamus, hippocampus, cerebellum) (*22*). The mSPECT was calculated from normal side basal ganglia slices (slice No., 31-40) of 3DSRT ROIs.

C-BUR and BUR-AS methods mBUR were calculated as Equation 3 using the AUC converted counts per square centimeter and mSPECT.

$$\mathrm{mBUR} = \frac{\mathrm{mSPECT} \cdot \mathrm{A}}{\text{AUC converted counts per square centimeter}} \qquad (3)$$

where A is cross calibration factor. The C-BUR and BUR-AS methods mCBF were calculated using a regression Equation 4 based on the ^{123}I-IMP microsphere method (*9*).

$$\mathrm{mCBF} = 13.2 \cdot \mathrm{mBUR}^{0.513} \qquad (4)$$

Figure 2 shows a flowchart indicating processing procedures of patlak plot and BUR-AS method.

Reproducibility evaluation

Patlak plot, C-BUR and BUR-AS methods mCBF were analyzed by three radiological technologists (RT). Inter- and intra-operator reproducibility estimated using the coefficient of variation (CV) and Bland-Altman plot with each mCBF obtained by three RTs. To estimate intra-operator reproducibility, three RTs were analyzed three times at intervals more than one month.

Statistical analysis

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, ver. 2.13.0) (*23*). The mCBF CVs were analyzed using Kruskal-Wallis test and the multiple comparisons among three methods were done with post hoc-Steel methodology (the non-parametric analog comparable to Dunnett test). In all analyses, $p < 0.05$ was considered to indicate statistical significance.

Results

Inter-operator reproducibility

The CV of patlak plot, C-BUR and BUR-AS methods mCBF were 0.039, 0.068 and 0.024, respectively (Figure 3). BUR-AS method had significantly lower CV than other methods (patlak plot and BUR-AS methods: p= 0.001, C-BUR and BUR-AS methods: p< 0.001). Difference of mCBF analyzed each operator for three methods are shown in Figure 4. The average difference of patlak plot, C-BUR and BUR-AS methods mCBF among three RTs were 0.9, 1.2 and -0.8, respectively. In addition, limits of agreement were -3.5 to 5.3, -8.1 to 10.4 and -3.8 to 2.3 for patlak plot, C-BUR and BUR-AS methods, respectively. As a result, BUR-AS method mCBF was smallest range among three methods. The case of worst reproducibility among three RTs in BUR-AS method is shown in Figure 5. The ROI setting of aortic arch, slice selection of dynamic images and range setting of TAC fitted gamma function among three RTs were difference.

Intra-operator reproducibility

The CV of patlak plot, C-BUR and BUR-AS methods mCBF among each RTs were 0.031, 0.024 and 0.010 for RT1, 0.028, 0.020 and 0.016 for RT2, 0.033, 0.035 and 0.022 for RT3, respectively (Figure 6). BUR-AS method had lowest mCBF of other methods in all RTs, however between C-BUR and BUR-AS methods for RT2, and between patlak plot and BUR-AS for RT3 were not shown significant difference (p= 0.40 and p= 0.057). Difference of each RTs mCBF are shown in Figure 7. The average difference of patlak plot, C-BUR and BUR-AS methods mCBF among three RTs were 0.3, -0.2 and -0.1, respectively. In addition, limits of agreement were -3.7 to 4.4, -4.3 to 3.9 and -2.6 to 2.5 for patlak plot, C-BUR and BUR-AS methods, respectively. As a result, BUR-AS method mCBF was smallest range among three methods.

Discussion

Patlak plot and BUR methods have examined as non-invasive brain perfusion quantitative measurement at many institution. Matsuda et al. have reported that the CBF of patlak plot method using ^{99m}Tc-HMPAO converts to ^{133}Xe CBF using regression expression (*4*). In addition, Matsuda et al. have reported that the CBF of patlak plot method using ^{99m}Tc-ECD correlated with it using ^{99m}Tc-HMPAO (*6*). Miyazaki et al. have reported that the CBF of BUR method using ^{99m}Tc-ECD correlated with the CBF of continuous arterial blood sampling method using ^{123}I-IMP (*9*). As clinical studies, Kuroda et al. have reported that CBF and cerebrovascular reactivity have derived from quantitative analysis methods of stress and rest brain perfusion SPECT using ^{99m}Tc-labeling agents are useful of staging diagnosis and treatment sections about carotid artery occlusion (*24-26*).

However, Otake et al. have reported manual ROI setting of aortic arch and bilateral brain hemispheres has difference by operators (*11*). These error are considered to influence indication for treatment and therapy evaluation of revascularization for cerebral ischemia. Therefore, we proposed to BUR-AS method aimed to improve reproducibility, and validated about inter- and intra- operator reproducibility.

In inter-operator reproducibility, BUR-AS method CV was lowest mCBF of other methods. Although patlak plot and C-BUR methods performed manual setting in all processing, BUR-AS method performed automatic processing except for the aortic arch ROI setting and a fitting of gamma function of TAC. Manual processing contribute to reduction of reproducibility, thus we considered that patlak plot and C-BUR methods were worth reproducibility than BUR-AS method. As a results, inter-operator reproducibility suggested that BUR-AS method is the best quantitative approach in three methods.

In intra-operator reproducibility, we compared intra-operator errors among three methods. BUR-AS method CV was the lowest mCBF of other method, however C-BUR method of RT2 and patlak plot method of RT3 were no significant difference compared with BUR-AS method. These reasons have two possible. One reason had high intra-reproducibility about patlak plot and C-BUR methods to have clear criteria by operators. As other reason, BUR-AS method had analysis error due to manual processing such as ROI setting of aortic arch, slice selection of dynamic images and range setting of TAC fitted gamma function. These problems are expected that those operators are improved by reconfirmation of those criteria. Furthermore, the most method to improve quantitative accuracy is to automate about all processing procedure of BUR method. Then, BUR-AS method was lowest variability in all mCBF area at Figure 7. Therefore, BUR-AS method suggested that best mCBF quantitative approach about intra-operator reproducibility.

This study have some limitations. One of the limitation wasn't automated the aortic arch ROI setting and a fitting of gamma function of TAC, so that BUR-AS method had analysis error in some cases. Odashima et al. have reported that reproducibility was improved by automating the ROI setting of aortic arch and TAC fitted gamma function in BUR method (*17*). Therefore, BUR-AS method is expected improvement of operator reproducibility using Odashima et al. method in this study. Secondly, our study is used for dynamic images of anterior view to compare patlak plot and BUR-AS methods in same patients. Inoue et al. have reported BUR method obtained a good correlation with continuous arterial blood sampling method of ^{123}I-IMP by change of ROI setting from aortic arch to ascending aorta and change of imaging position from anterior view to left anterior oblique (LAO) 10° view (*15*). Moreover, Ito et al. have also reported that a good correlation with $H_2{}^{15}O$ PET using LAO view and ascending aorta ROI setting (*16*). If the dynamic data acquired the LAO 10° view to separate ascending aorta and descending aorta, the ROI readily set on ascending aorta, so that BUR-AS method is expected the improvements of inter- and intra- operator reproducibility. Finally, the improvement of inter- and intra- operator reproducibility about CBF quantitative analysis will be expected to increase of diagnostic accuracy about follow-up and determination of treatment adaptation.

Conclusions

We verified about inter- and intra- operator reproducibility by comparison of patlak plot, C-BUR and BUR-AS methods. BUR-AS method mCBF had highest reproducibility of other method. As a result, we were demonstrated that BUR-AS method can provide a stable cerebral blood flow to have high inter- and intra- operator reproducibility, compared to patlak plot and C-BUR methods.

We reported a part of this study in annual congress of the European association of nuclear medicine, October 21,2014, Gothenburg, Sweden.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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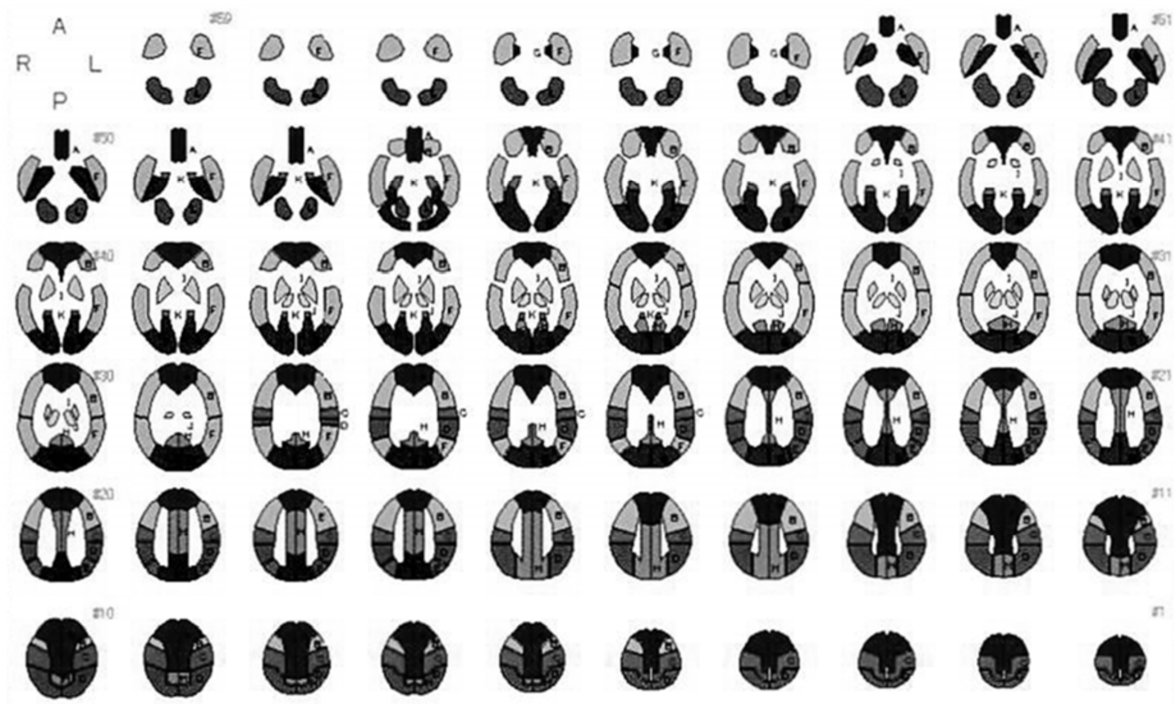

FIGURE 1

Standardized ROIs using three-dimensional stereotaxic ROI template (3DSRT).

ROIs were set on each side in image slice standardized using 3DSRT composed of 12 segments (callosomarginal, precentral, central, parietal, angular, temporal, posterior cerebral, pericallosal, lenticular nucleus, thalamus, hippocampus, cerebellum).

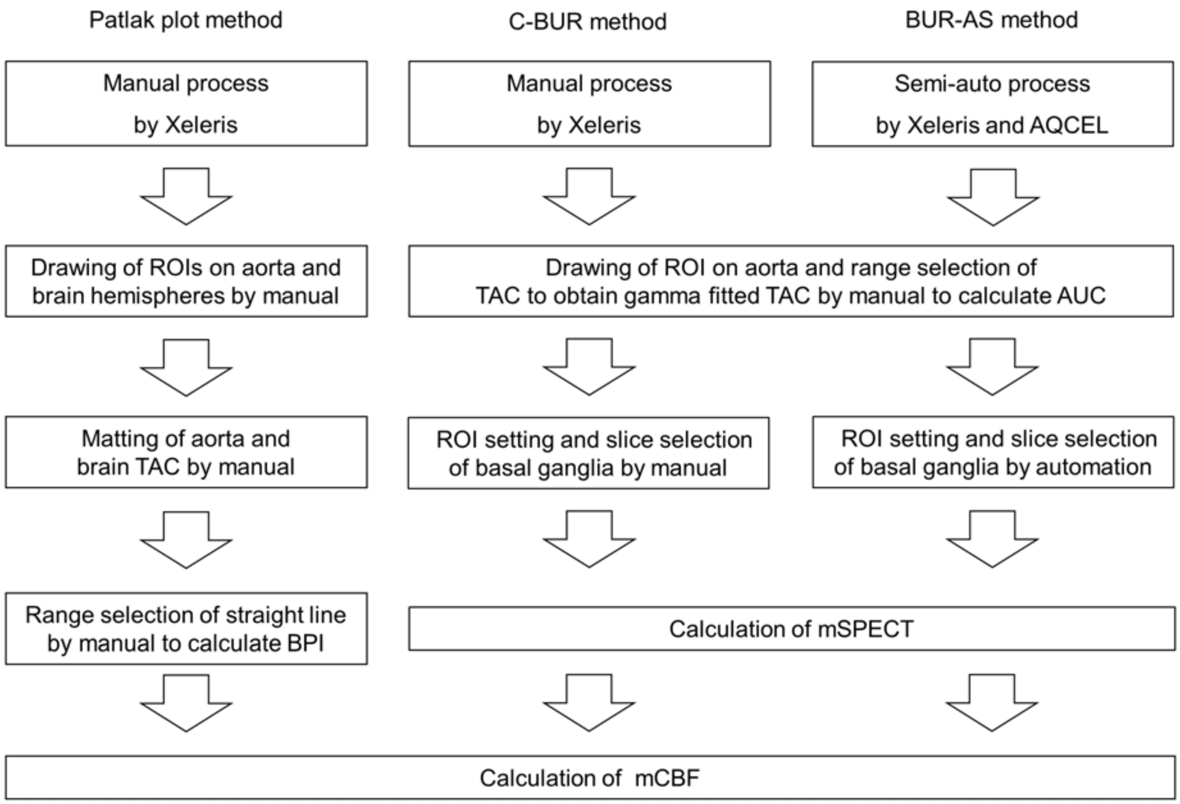

FIGURE 2

Flow chart of cerebral blood flow SPECT quantitative analysis process procedure.

The flow chart shows cerebral blood flow SPECT quantitative analysis process procedure of patlak plot, C-BUR and BUR-AS methods. Patlak plot and C-BUR method has been processed by all manually. BUR-AS method mCBF has been processed aorta ROI and range selection of TAC by manually, ROI setting and slice selection of basal ganglia by automation.

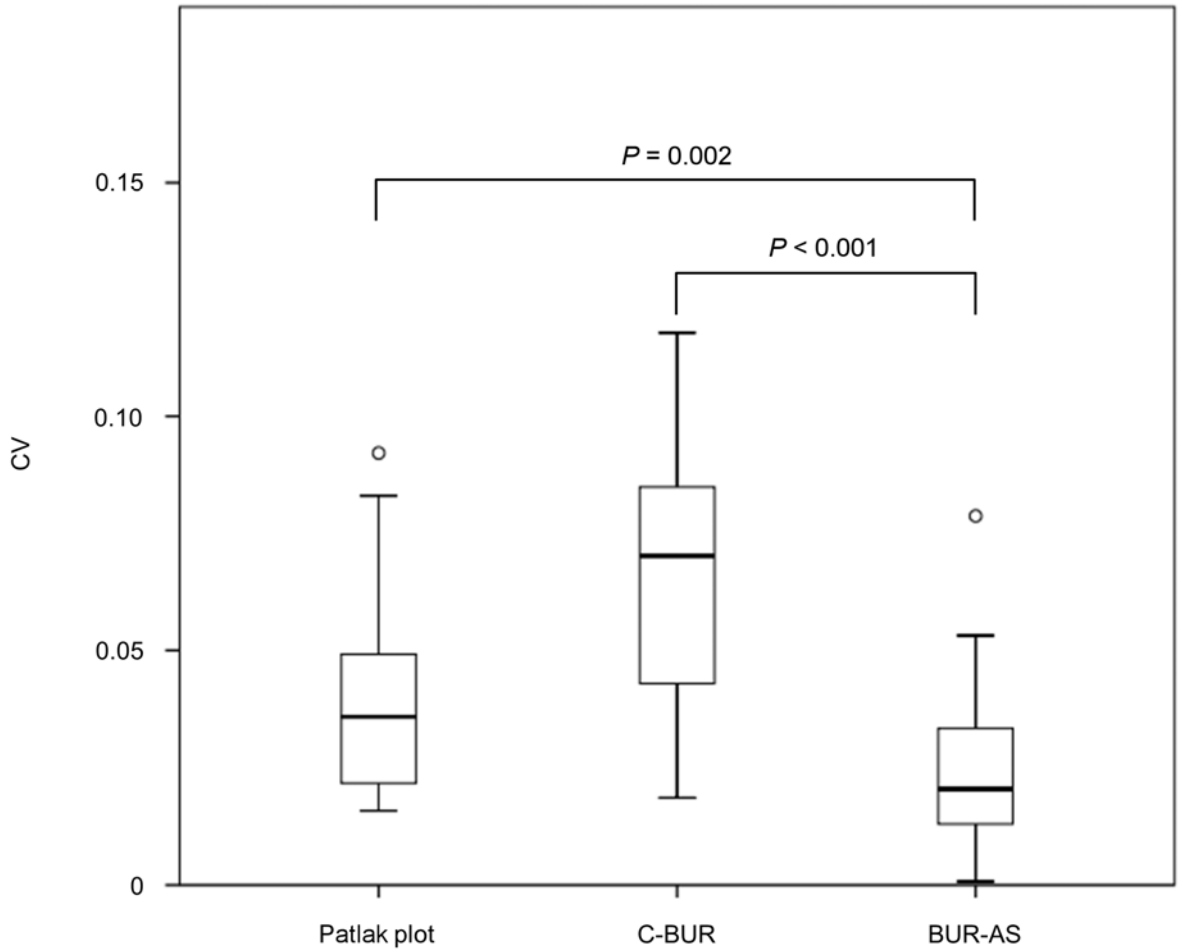

FIGURE 3

The figure is shown on the coefficient of variation (CV) of three methods mCBF (left: patlak plot, middle: C-BUR, right: BUR-AS) for inter-operator reproducibility. The CV of BUR-AS method mCBF had significantly lowest one of other method.

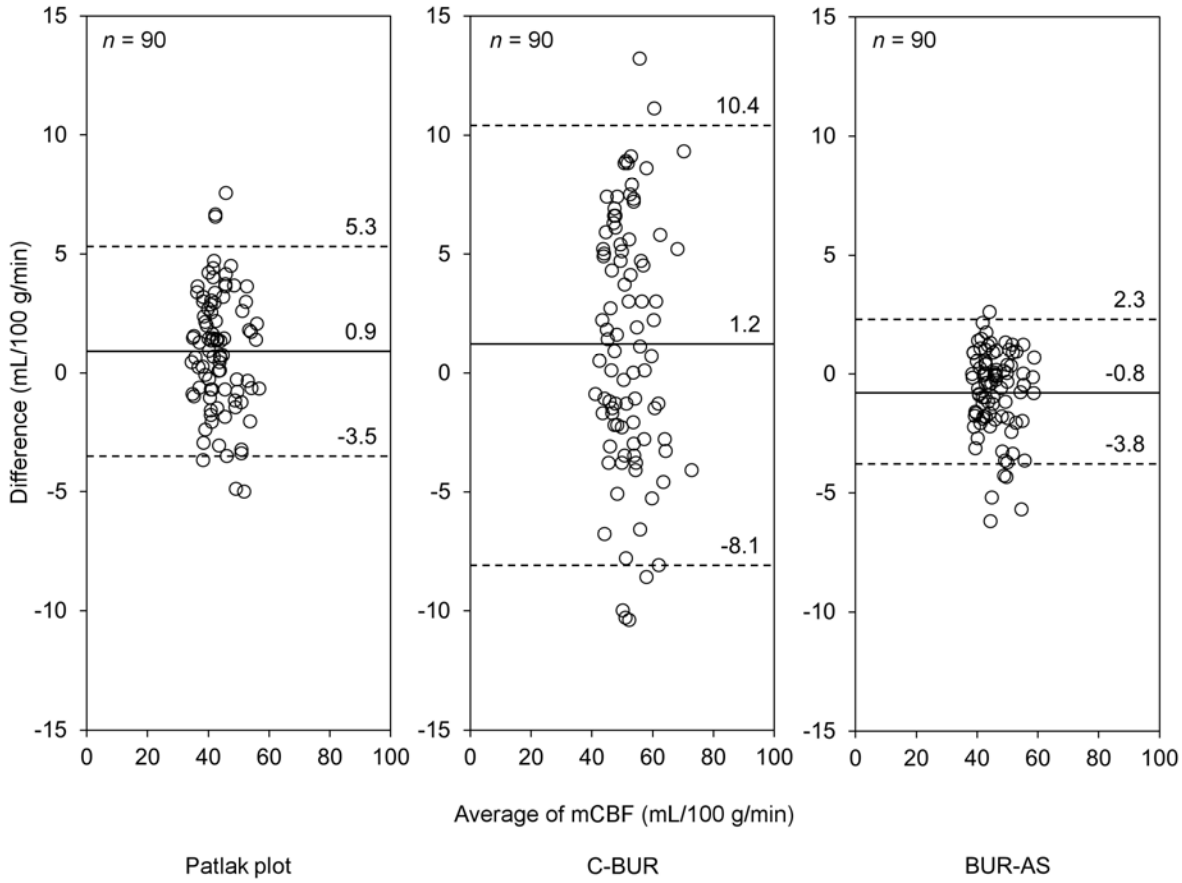

FIGURE 4

Bland-Altman plots for inter-operator reproducibility of mCBF of three methods (left: patlak plot, middle: C-BUR, right: BUR-AS).

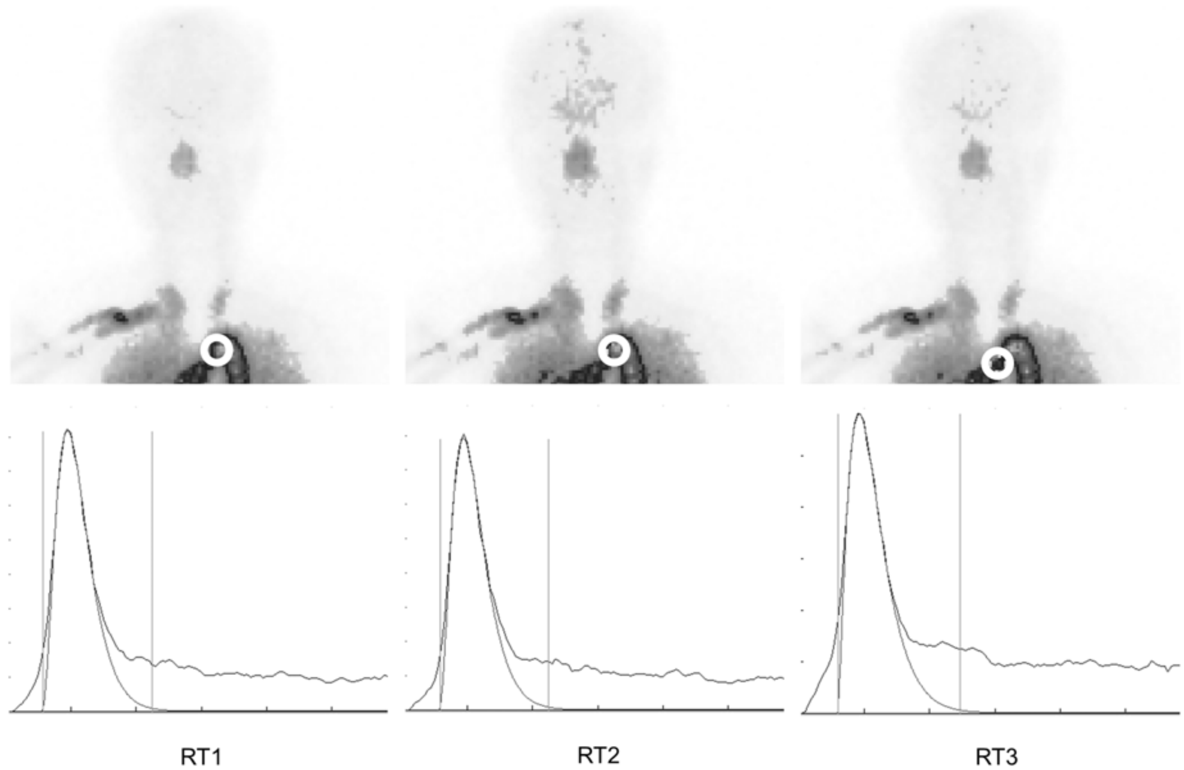

FIGURE 5

An example setting of region of interest (ROI) and gamma fitting of three RTs. The upper row each images indicates the dynamic images slice and ROI setting from each RTs have selected (left: RT1, middle: RT2, right: RT3).

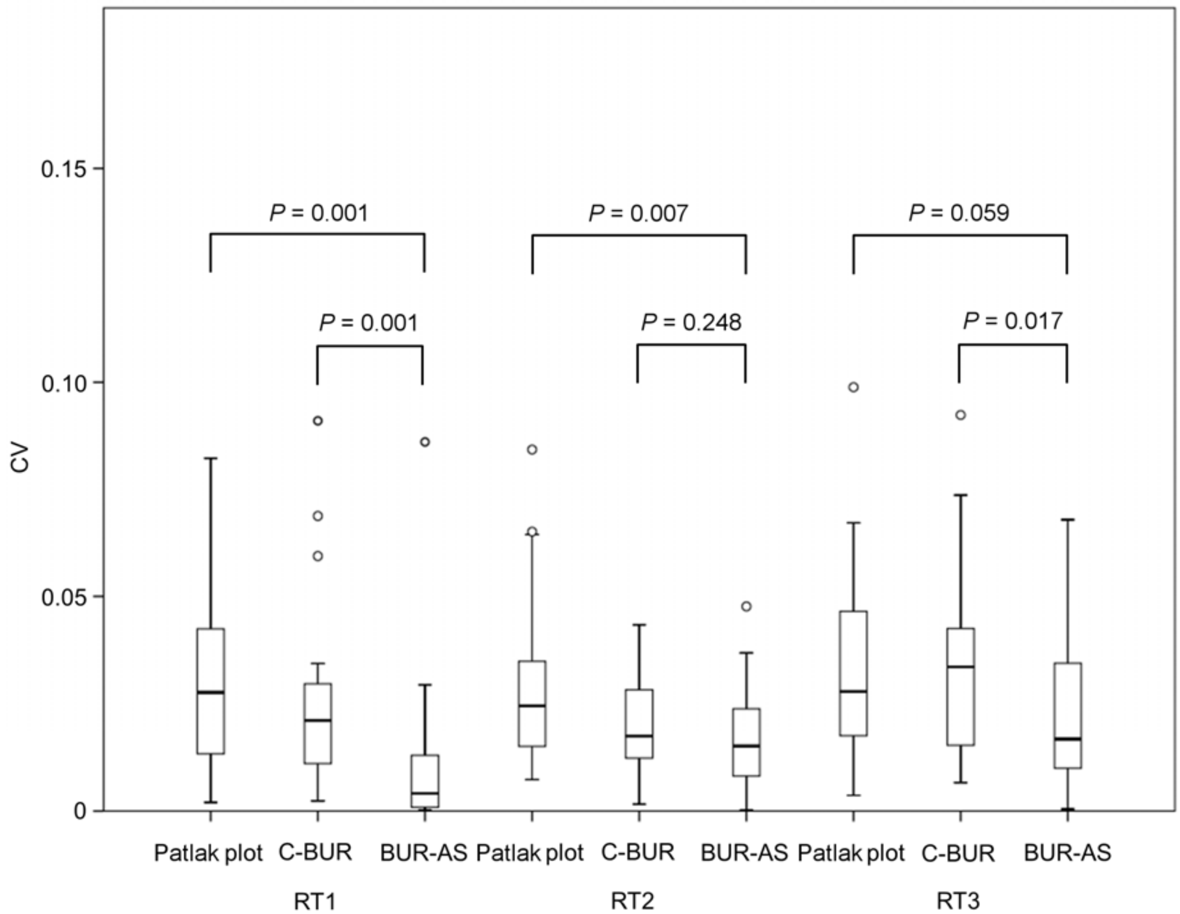

FIGURE 6

The figure is shown on the coefficient of variation (CV) of three methods mCBF (left: patlak plot, middle: C-BUR, right: BUR-AS) for intra-operator reproducibility. The CV of BUR-AS method mCBF had lowest one of other method, but The CV of C-BUR for RT2 and patlak plot for RT3 were no significant difference.

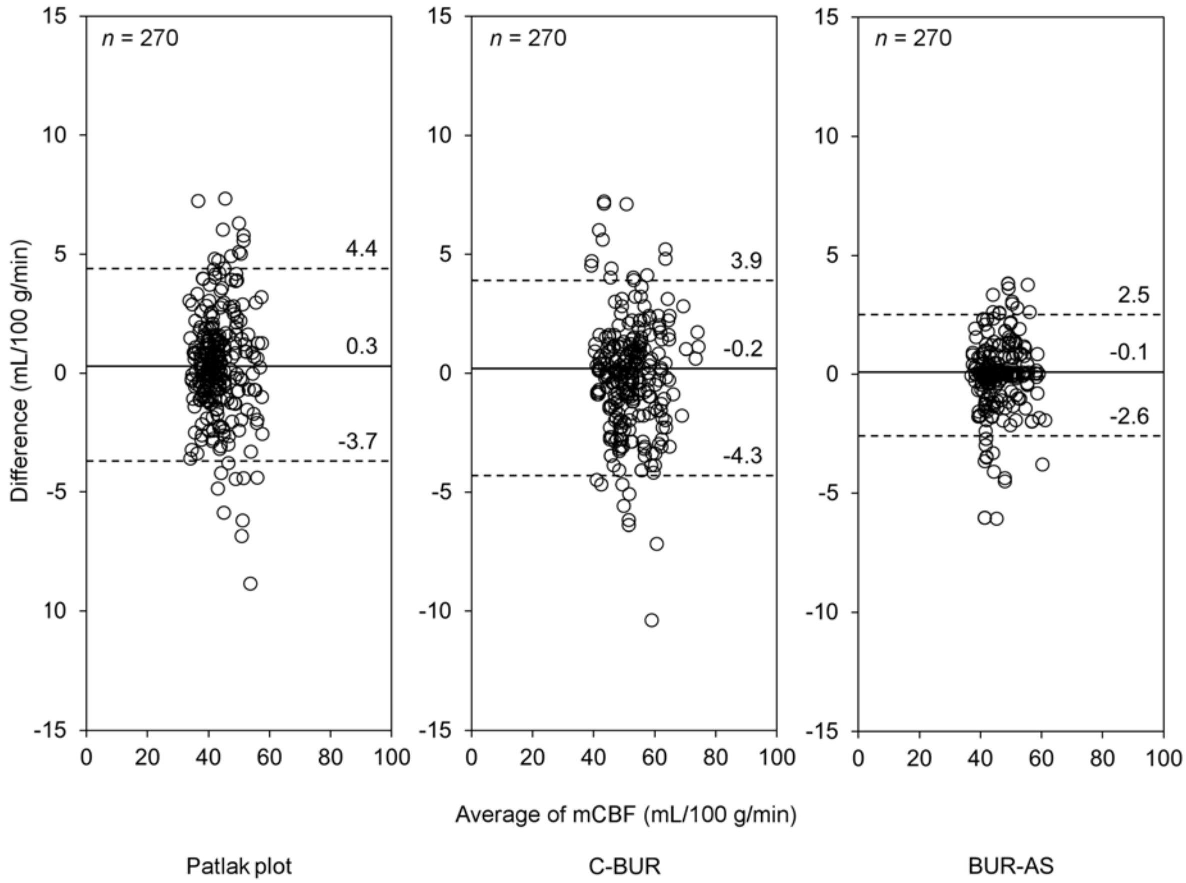

FIGURE 7

Bland-Altman plots for intra-operator reproducibility of mCBF of three methods (left: patlak plot, middle: C-BUR, right: BUR-AS).