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A New Approach for Simple Radionuclide Cisternography Examination in Cerebrospinal Fluid Leakage Detection

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ABSTRACT

Objective We developed a new quantitative interpretation technique of radioisotope cisternography (RIC) for the diagnosis of spontaneous cerebrospinal fluid hypovolemia (SCH).

Methods RIC studies performed for suspected SCH were evaluated. ^{111}In-DTPA RIC images were taken at 0, 1, 3, 6 and 24-hours after radioisotope injection following the current protocol. Regions of interest (ROI) were selected on 3-hour images to include brain, spine, bladder or the whole body. The accumulative radioactivity counts were calculated for quantitative analysis. Final diagnoses of SCH were established based on the diagnostic criteria recently proposed by Schievink and colleagues.

Results Thirty-five patients were focused on. Twenty-one (60.0%) patients were diagnosed as having SCH according to the Schievink criteria. On the 3-hour images, direct cerebrospinal fluid (CSF) leakage sign was detected in nine of 21 SCH patients (42.9%), as well as three patients with suspected iatrogenic leakage. Compared to non-SCH patients, SCH patients showed higher bladder accumulation at 3-hour images (P=0.0002), and higher brain clearance between the 6-hour and 24-hour images (P<0.0001). In particular, the 24-hour brain clearance was more conclusive for the diagnosis than 24-hour whole cistern clearance. The combination of direct sign and 24-hour brain accumulation resulted in 100% of accuracy in the 32 patients in whom iatrogenic leakage was not observed. 1- and 6-hour images did not provide any additional information in any patients.

Conclusions A new simple ROI setting method, in which only the 3-hour whole body and 24-hour brain images were necessary, was sufficient to diagnose SCH.

Keywords

Spontaneous cerebrospinal fluid hypovolemia; Radioisotope cisternography; Quantitative analysis; Simple radioisotope cisternography examination protocol.

BACKGROUND

Spontaneous cerebrospinal fluid hypovolemia (SCH) caused by spontaneous leaks of CSF is characterized by prominent orthostatic headache associated with neck stiffness, tinnitus, hypoacusia, and often photophobia and nausea [1-10]. SCH is an important headache etiology particularly in young and middle-aged individuals, but an initial misdiagnosis such as migraine, tension headache or viral meningitis, is common [4].

Brain magnetic resonance (MR) imaging may show characteristic features of SCH, including subdural fluid collections, enhancement of the pachymeninges, engorgement of venous structures, pituitary hyperemia, and sagging of the brain [4,9]. Nonetheless, even in a patient whose spinal CSF leak is confirmed by contrast-enhanced computed tomography (CT) myelography, brain MR imaging may show no abnormal findings [11]. CT myelography of the entire spine combined with or without MR myelography has been shown to be useful in detecting location and extent of a CSF leak. On these modalities most spinal CSF leaks are located at the cervicothoracic junction or in the thoracic spine and may be associated with meningeal diverticula [4,12]. In such cases, CT myelography may depict meningeal diverticula but cannot exclude CSF leakage. In contrast, 24-hour radioisotope accumulation on the whole cistern is definitive to rule out CSF leakage in meningeal diverticula cases [13].

Moreover, a relatively high radiation dose is an inevitable shortcoming of CT myelography. Radiation dose exposure of ^{111}In radioisotope cisternography (RIC) is 5 mSv at most while radiation from CT myelography may expose the spinal cord to up to eight times more [14]. While MR myelography has a high rate of leak detection and appears safe in small doses for myelography [15,16], intrathecal administration of gadolinium contrast medium is considered an off-label use all around the world.

In Japan, a study group named "The Establishment of Diagnosis and Therapy for Cerebrospinal Fluid Hypovolemia" organized by The Ministry of Health, Labour and Welfare is continuously collaborating with several neurology and neurosurgery associations to establish diagnostic criteria including imaging criteria for SCH [17]. In this recommendation, the benefits of RIC were emphasized. Moreover, RIC is considered as the first imaging workup for SCH suspects, due to its capability to provide whole body screening data using a simple procedure and short scan time. RIC is a very helpful modality to evaluate patients who are suspected of having spontaneous CSF leaks. In particular, RIC has a significant role in atypical and doubtful cases when it is required to decide whether a leak does or does not exist [13].

In some cases, RIC might detect CSF leakage into the epidural space (direct sign) [1,2,6,9,18,19]. However, the direct sign might not be observed even in cases highly suggestive for SCH, with the likely explanation being that the leak volume is below the sensitivity limit of the gamma camera. In such cases, early bladder accumulation and faster radioisotope clearance indicate early absorption into the epidural venous system through abnormal leaks, which are useful as indirect signs establishing a diagnosis of SCH [7,18,20]. The use of these indirect signs has encouraged the introduction of several quantitative approaches to improve diagnostic accuracy [2,13,19,21].

In clinical practice, RIC has not been widely accepted as a diagnostic tool for SCH because of several limitations: 1) differentiating true pathological leakage from iatrogenic (injection-related) CSF leakage can be difficult, 2) there is no consensus on the ROI setting, and 3) serial image acquisitions are required for up to 24 hours, resulting in a very time-consuming examination. To address these problems, we evaluated a novel approach to simplifying the RIC examination protocol while maintaining diagnostic accuracy.

METHODS

Patients

This retrospective study involves 35 patients (15 male and 20 female; age, 38.6±13.2, range, 13-70 years old) who had orthostatic headache suspicious for SCH and had undergone RIC examination during the six-year period from June 2007 to June 2013. The associated symptoms were tinnitus (5), hypacusia (10), photophobia (6), nausea (9), dizziness (7) and neck pain (12). Eighteen patients had a posttraumatic headache, and 17 did not have a history of trauma. All patients underwent RIC examinations and brain MR imaging with gadolinium contrast enhancement (Gadopentetate Meglumine acid, 0.1 mmol/kg body weight; Magnevist®, Bayer Yakuhin Ltd., Osaka, Japan). Two patients also received CT myelography. Of 35 patients, 23 underwent epidural blood patch (EBP) performed by a well-experienced neurosurgeon (20-years' experience). This study was approved by the institutional review board of Gunma University and Japan Red Cross Society Maebashi Hospital, and informed consent was waived due to its retrospective nature.

Diagnosis of SCH

The final diagnosis of CSF leakage was established based on the diagnostic criteria for a headache due to SCH, recently proposed by Schievink and colleagues (**Table 1**) [22], which does not include RIC examination.

Imaging Protocol of RIC examination

Just before imaging examinations, patients were asked to empty their bladders, and their vital signs were checked. Each patient was placed in the right lateral decubitus position, and a 22G or 25G spinal needle [21] was intrathecally inserted at the L4/5 level. CSF was collected, and CSF pressure was measured whenever possible. Then, a dose of 37 MBq ^{111}In-diethylene triamine pentaacetic acid (^{111}In-DTPA, Nihon Medi-Physics Co., Ltd., Tokyo, Japan) was administered, immediately followed by anterior-posterior and head-to-knee image acquisitions (0-hour images). Three hours bed rest following the injection was routinely ordered, and 1, 3, 6 and 24-hour image acquisitions were performed in the same manner. Patients were instructed to resist urinating until the 3-hour image acquisition was completed. On 3-hour and 6-hour acquisitions, additional right and left lateral view images were acquired. RIC images were taken with auto-contour scan at 15 cm/min using a gamma camera system (e.cam Siemens Medical Solutions, Illinois) with medium energy collimator.

Image Analysis

The 3-hour image was selected for ROI selection due to its uniform radioactivity distribution in all organs, which is required for accurate manual ROI drawing over the brain (*Br*), spine (*Sp*), bladder (*Bl*) and whole body (*WB*) (**Fig. 1**). This cannot be done to RIC images obtained earlier than 3 hours, in which a very high radioactivity count pools mainly at the injection site, exceeding the upper reading limit of the gamma camera. The whole body ROI (a rectangle covering the entire scan field) on the 3-hour image was used as a reference for the total count. Decay-corrected count to 0-hour was measured for each ROI. Time-activity curves (TAC) of the brain, whole cistern (brain plus spine), and bladder were constructed.

A single rectangular ROI covering the brain and spine has been employed in previous studies [19,21,23]. Instead of it, in this study two rectangular ROIs were drawn manually: 1) The height of the brain ROI was the distance from the vertex to the top of the first cervical vertebra on the patient's sagittal brain MRI image. The ROI width was the lateral extent of the uptake. 2) The spinal ROI was drawn from the lower border of the brain ROI through the cauda equina, with the width extended as far as possible without including the kidney uptakes. The rectangular bladder ROI was drawn tightly covering the bladder uptake. ROI settings were first performed on both anterior and posterior views of 3-hour images, and ROIs with the same shape and location were set on 0, 1, 6, and 24-hour images. Quantitative parameters (radioactivity increment in the bladder and count decrease in the whole cistern) were calculated based on the count in each ROI using the following formulae:

$$\text{Total count} = \frac{\left(WB_{ant} + WB_{post}\right)_{\text{at 3 h}}}{exp\left(-0.693\times\frac{3}{67.92}\right)}\times 100\%$$

3 is the acquisition time (in h) and 67.92 is the half life (in h) of ^{111}In.

$$\text{Bladder accumulation at } t \text{ h} = \frac{(Bl_{ant} + Bl_{post})_{\text{at } t \text{ h}}}{\text{Total Count}} \times 100\%$$

$$\text{Brain accumulation at } t \text{ h} = \frac{(Br_{ant} + Br_{post})_{\text{at } t \text{ h}}}{\text{Total Count}} \times 100\%$$

Whole Cistern accumulation at t h

$$= \frac{(Br_{ant} + Br_{post} + Sp_{ant} + Sp_{post})_{\text{at } t \text{ h}}}{\text{Total Count}} \times 100\%$$

Particular points to be evaluated were: 1) the ideal acquisition time and patient position to confirm direct CSF leakage signs; 2) comparison of the total count on 0 hour RIC images (both anterior and posterior images) and the decay-corrected total count on 3 hour images; 3) time-activity curve of bladder up to 3 hours after injection, and 4) accumulation of the whole cistern and brain within 6 and 24 hours. CSF leak was evaluated by a nuclear medicine physician (TH) with 20 years of experience by reviewing all RIC images.

Statistical analyses

The values were expressed as mean ± standard deviation (SD). Wilcoxon signed-rank test, Mann-Whitney analysis and ROC analysis were employed. Statistical analysis and the graph were calculated and prepared using Prism version 6.0.9 for Mac OS X (GraphPad Software, Inc.). For all statistical analyses, *P* values less than 0.05 were considered statistically significant.

RESULTS

<u>Patients' diagnoses and treatments</u>

Clinical and radiographic features of the patients were summarized in **Table 1**. Nine (25.7%) of 35 patients had low opening pressure, 23 (65.7%) patients had sustained improvement of symptoms after EBP, and 20 (57.1%) patients had abnormal MRI findings. Twenty-one (60.0%) of 35 patients met the Schievink criteria and were diagnosed with SCH [22].

<u>RIC image findings</u>

1) Total Count Determination

There was no significant difference between the decay-corrected total count on the 3-hour RIC image ($1.5\pm0.3*10^6$; range, $0.7\text{-}1.9*10^6$), compared to the total count on the 0-hour RIC image ($1.5\pm0.3 *10^6$; range, $0.7\text{-}2.0*10^6$; P=0.326).

2) Iatrogenic leakage

Three patients with iatrogenic leakage found in this study showed rapid and obviously higher (more than 40%) bladder accumulation on the 3-hour RIC images compared to the remaining patients (**Fig. 2a**). The whole cistern accumulation was obviously lower compared to the remaining patients on the 3-hour RIC images (**Fig. 2b**). These differences were apparent on visual assessment of the 3-hour RIC images: the cistern accumulation was imperceptive, and a striking bladder accumulation was observed (**Fig. 3**). Increased background radioactivity was another finding suggesting iatrogenic leakage. These three cases were excluded from further analyses.

3) Direct signs of CSF leakage

CSF leakage (direct sign) was visualized in nine (28.1%) of 32 patients on the 3-hour RIC images (**Fig. 4**). Lateral view acquisition helped to depict these direct signs in two patients. In seven of nine patients, the leakages were seen at the height of the thoracic vertebra (3) and the lumbar vertebra (4). In two other patients, the leakages were seen at both the head and the cervical vertebra, or from the both cervical and lumbar vertebra. CSF leakages were also observed on the 6-hour RIC images in two patients while in the remaining seven patients the leaks became unclear. The 1-hour and 24-hour RIC images did not provide any additional information of the direct sign.

<u>TAC curve analyses and indirect sign of CSF leakage</u>

1) Bladder accumulation rate on the 3-hour RIC images

Bladder accumulation rates in SCH cases were significantly higher than non-SCH cases (P=0.0002; **Fig. 5**). The area under curve (AUC) in receiver operating characteristic (ROC) analysis of the bladder accumulation rate on 3-hour RIC images was 0.86 with a sensitivity of 0.72 and specificity of 0.86 (cutoff value=7.64).

2) Whole cistern and brain accumulation rate, and appropriate evaluation time for SCH diagnosis

The TAC of the whole cistern accumulation showed that SCH patients had a significantly lower accumulation rate on 1, 3, 6, and 24-hour RIC images (P=0.02, 0.0004, 0.0004 and 0.0001, respectively) compared to non-SCH patients (**Fig. 6a**). On 24-hour RIC images, AUC was 0.90 with sensitivity of 0.89 and specificity of 0.93 (cutoff value=16.13), and 0.87, 0.83, 0.79 (58.6) on 6-hour; 0.87, 0.83, 0.86 (74.7) on 3-hour images, and 0.75, 0.67, 0.79 (82.9) on 1-hour images, respectively (**Fig. 6b**).

The TAC of the brain accumulation showed that the SCH patients had a significantly lower accumulation rate on 6-hour and 24-hour RIC images ($P=0.0003$ and $P<0.0001$, respectively) compared to non-SCH patients, but showed no significant differences on 1- and 3-hour RIC images (**Fig. 7a**). AUC was 0.92 with sensitivity of 0.89 and specificity of 0.93 (cutoff value=12.75) on 24-hour RIC images, and 0.88, 0.89, 0.93 (13.29) respectively on 6-hour RIC images (**Fig. 7b**).

SCH patients were best differentiated from non-SCH patients by the 24-hour brain accumulation rate (AUC=0.92; cutoff value=12.75, sensitivity=0.89, specificity=0.93). If the diagnosis of SCH was made when either direct or indirect sign was positive, the sensitivity and specificity were both 1.0 in the current 32 patients. Area under curve (AUC) values were compared by the method of Hanley and McNeil. The AUC values of 24-hour RIC images in the whole cistern and the brain were not significantly different (p-value = 0.80).

DISCUSSION

This study's results showed that the 3-hour RIC image could depict the direct sign and exclude iatrogenic leakage, while the 24-hour RIC images of brain accumulation could show indirect signs. A combination of the direct sign and the 24-hour brain accumulation was the most conclusive for SCH diagnosis. The 24-hour brain accumulation was a useful indicator in cases with no or unclear direct sign. In addition, our analyses revealed that the accompanying 0, 1 and 6-hour RIC images did not provide any additional information to establish SCH diagnosis.

The diagnosis of SCH has been based on detection of CSF leakage or indirect signs, i.e. early bladder visualization and faster radioisotope clearance from the whole cistern. Since the direct sign is occasionally unclear and not conclusive because of poor spatial resolution, indirect signs have been commonly used to establish the diagnosis [24]. However, it has been reported that early bladder visualization may also be noted in patients without CSF leakage such as those with normal pressure hydrocephalus (NPH). Early bladder visualization related to iatrogenic leakage should also be carefully differentiated from SCH [2,3,9,12]. Serial blood sampling has been reported to be useful in excluding iatrogenic leakage, with blood radioactivity peak around two hours being pathognomonic [2]. However, it is time-consuming and impractical in clinical practice.

One of the challenges in a quantitative approach to utilizing indirect signs is the ROI setting, which varied in previous reports. For example, Moriyama and colleagues set the ROI on the whole cerebrospinal field including the kidneys [19,23]. In our study, multiple ROIs for brain, spine and bladder were drawn to allow distinct evaluation. The assessment of ROI counts is another challenge. Although mathematical exponential fitting might be accurate for evaluating the changes of radioactivity [19], the procedure is time-consuming and complicated. Instead, we adopted a simple clearance or accumulation rate calculation.

Previously reported methods require at least five image acquisitions (at 0, 1, 3, 6 and 24 hours after injection) [2,19,21,23]. However, we found that SCH diagnosis, as well as iatrogenic leakage exclusion, can be established without performing 0, 1 and 6-hour acquisitions (**Fig. 6**). The 3-hour RIC image can replace the 0-hour RIC image as a reference for the total count since its decay-corrected count was not significantly different to the total count on the 0-hour RIC image. This means that ^{111}In-DTPA does not need to be injected in the radioisotope examination room (under the gamma camera system), which can improve examination room turnover.

This phenomenon can be explained by the physiological metabolism of CSF. With a constant CSF production rate of 500 mL/day, a similar absorption rate is required to maintain constant volume of 160 mL in the whole cistern compartment, resulting in an outflow rate of 21 mL/hour. For that reason, in normal circumstances and uniform distribution of injected radioisotope (1 mL) within the intact cistern compartment, accumulation of radioisotope outflow (in blood circulation and bladder) after 3 hours should not exceed 39.4% ([3 hour*21 mL/hour] /160 mL*100(%)). Our three iatrogenic leakage cases were consistent with this hypothesis.

In this study, we found that 24-hour brain CR images were sufficient to differentiate SCH cases from non-SCH cases, and the count of the whole cistern accumulation may not be necessary. In fact, the ROI setting of the whole spine is frequently complicated by its non-linear form (such as in scoliosis) and kidney uptake involvement. Moreover, it is also known that transit time of CSF within the cistern may vary among individuals and is susceptible to other factors like patient position and activity after radioisotope injection.

Our study provides a robust scientific evidence of the superiority of 24-hour brain accumulation for SCH diagnosis with a statistically acceptable number of patients compared to the previous studies. A similar tendency was observed in a case series study with five patients [25] and a case report [1], both of which were published more than a decade ago. Our finding also supports the experience of one center where RIC for CSH diagnosis were intensively studied within the last 25 years [13].

The very low incidence of SCH (estimated 5 per 100,000 population) and the less frequent use of RIC recently represent actual challenges to any study related to the diagnostic use of RIC for SCH [4]. Therefore, the primary limitation of this study is the number of patients (n = 35). A future study with more participants may give us a more comprehensive understanding of the diagnosis of SCH using this technique.

CONCLUSIONS

The diagnosis of SCH can be established simply by detection of a direct sign or quantification of the 3-hour bladder accumulation and the 24-hour brain accumulation rate, while 0, 1 and 6-hour RC image acquisitions as encouraged in the current protocol may not provide additional information.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Table 1. Clinical and radiographic findings in 35 patients with SCH suspect diagnosis. [22]

Findings	No. of patients
A) Orthostatic headache	29
B) Presence of at least one of the following	29
Low opening pressure (≦60mmH_2O)	9
Sustained improvement of symptoms after EBP	3
Demonstration of an active spinal CSF leak on CT myelography *	2
Cranial MRI changes of intracranial hypotension	20
Subdural fluid collections	6
Enhancement of the pachymeninges	15
Engorgement of venous structures	4
Pituitary hyperemia	10
Sagging of the brain	18
C) No recent history of dural puncture	34
D) Not attributable to another disorder	25

* The two patients who underwent CT myelography showed direct CSF leakages.

FIGURE LEGENDS

Figs. 1. ROIs drawn on the 3-hour RIC images for the brain, spine, bladder and whole body.

Figs. 2. Bladder accumulation rate on the 3-hour RIC images and TAC of the whole cistern accumulation suggesting iatrogenic leakage. **(a)** Comparison of the 3-hour RIC images between patients with and without iatrogenic leakage. **(b)** TAC of the whole cistern accumulation up to 3 hours.

Both high bladder accumulation and low whole cistern accumulation on the 3-hour RIC images suggested iatrogenic leakage.

Fig. 3. Representative image of the direct sign on the 3-hour RIC image of iatrogenic leakage.

Note the very high bladder accumulation with no apparent cistern accumulation. Relatively high background accumulation was also seen.

Fig. 4. Representative image of the direct sign on the 3-hour RIC image.

Direct sign of CSF leakage is usually characterized by leakage from one side. (arrows). [3,9,19]

Fig. 5. Comparison of bladder accumulation rate at 3-hour RIC images between SCH and non-SCH patients.

Bladder accumulation rate of the SCH patients was significantly higher than that of the non-SCH patients (P=0.002).

Figs. 6. TACs of the whole cistern accumulation rate, and ROC analyses for the diagnosis of SCH. **(a)** TAC of the whole cistern accumulation rate. **(b)** ROC analysis of the whole cistern accumulation.

On the 24-hour RIC images, AUC was 0.90 with a sensitivity of 0.89 and specificity of 0.93 (cutoff value=16.13).

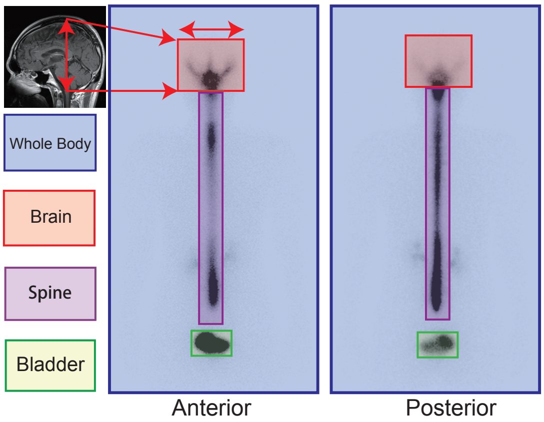
Figs. 7. TACs of the brain accumulation rate, and ROC analyses for the diagnosis of SCH. **(a)** TAC of brain accumulation rate. **(b)** ROC analysis of brain accumulation.

On the 24-hour RIC images, AUC was 0.92 with a sensitivity of

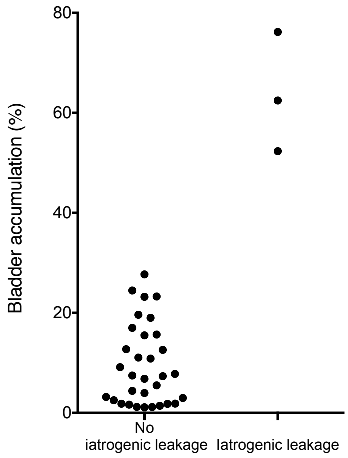
0.89 and specificity of 0.93 (cutoff value=12.75). The SCH patients were best differentiated from non-SCH patients by the 24-hour brain accumulation rate.

Fig. 8. The proposed RIC protocol for CFH diagnosis compared to the current protocol.

Figs.1.



Figs.2.(a)



Figs.2.(b)

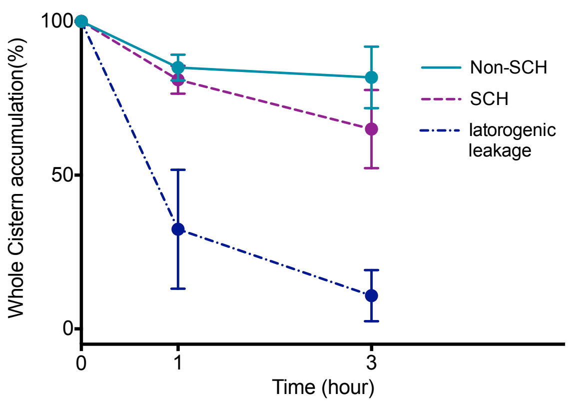
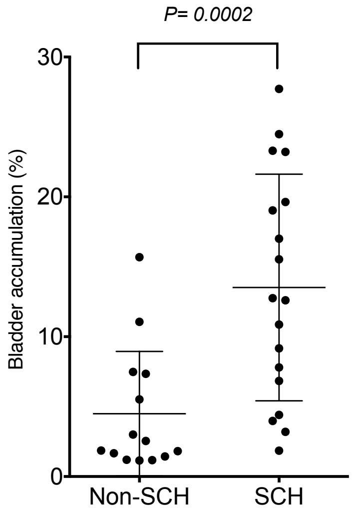


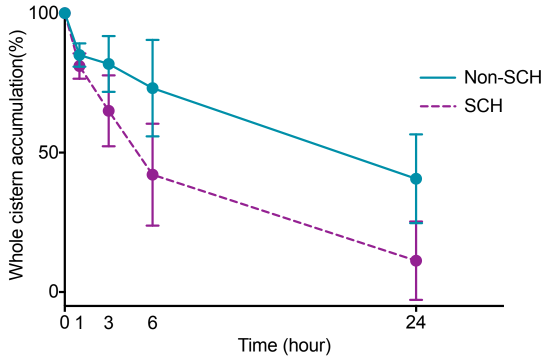
Fig.3.

Fig.4.

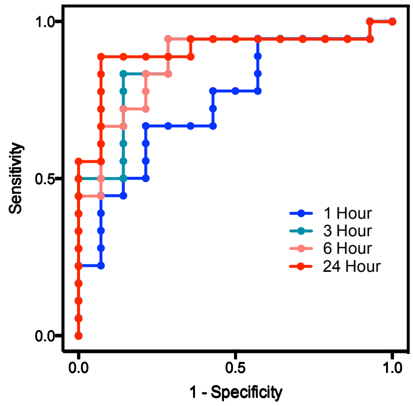
Fig.5.



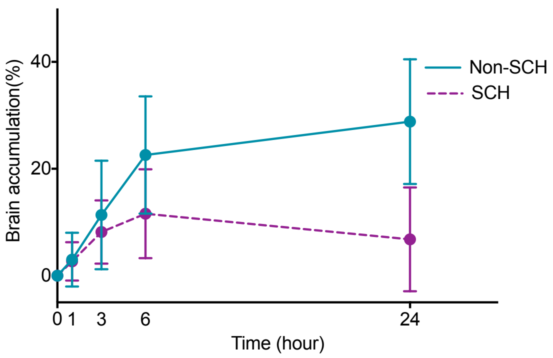
Figs.6.(a)



Figs.6.(b)



Figs.7.(a)



Figs.7.(b)

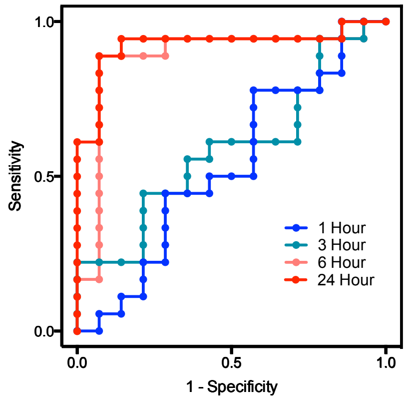
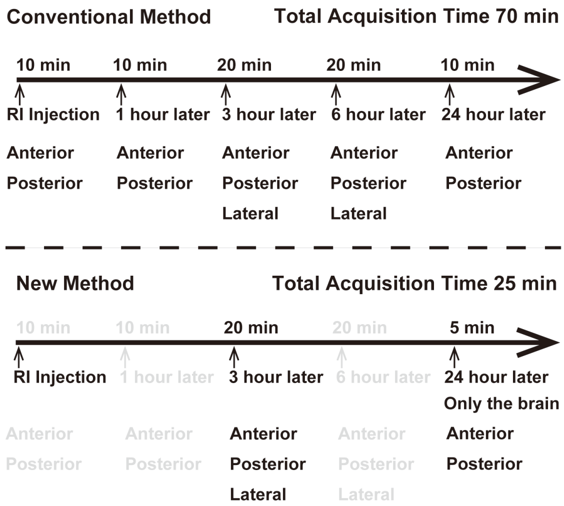


Fig.8.


Conventional Method
Total Acquisition Time 70 min
10 min
10 min
20 min
20 min
10 min
RI Injection
1 hour later
3 hour later
6 hour later
24 hour later
Anterior
Posterior
Anterior
Posterior
Anterior
Posterior
Lateral
Anterior
Posterior
Lateral
Anterior
Posterior
New Method
Total Acquisition Time 25 min
10 min
10 min
20 min
20 min
5 min
RI Injection
1 hour later
3 hour later
6 hour later
24 hour later
Only the brain
Anterior
Posterior
Anterior
Posterior
Anterior
Posterior
Lateral
Anterior
Posterior
Lateral
Anterior
Posterior