

Procedure Guidelines for CT/MR Perfusion Imaging 2006

Joint Committee for the Procedure Guidelines for CT/MR Perfusion Imaging

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Drafting Organization

Joint Committee for the Procedure Guidelines for CT/MR Perfusion Imaging

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Foreword

Computerized tomography (CT) perfusion imaging (CTP) and magnetic resonance (MR) perfusion imaging (MRP) (perfusion-weighted imaging: PWI) are examination methods that are used to scan the brain continuously during the rapid intravenous infusion of a contrast medium. These modalities aim to analyze the cerebral circulation based on time-course changes in the concentration of the contrast medium or signal intensity. These methods are relatively simple and easy compared with the conventional modalities of examining cerebral circulation. In addition, they can be performed immediately after noncontrast CT or diffusion-weighted imaging (DWI). Thus, CTP and MRP are now widely used for the evaluation of acute ischemic stroke in clinical practice.

CTP and MRP data provide a mine of information on the pathophysiology of acute stroke. At present, however, there is insufficient evidence or lack of high-quality scientific evidence supporting the clinical efficacy of these modalities, and their significance in thrombolytic therapy has not yet been fully revealed. Furthermore, the methods of examination/analysis/evaluation are considerably different depending on the institutions where they are performed and the equipment used. In addition, standard procedures for these modalities have not yet been established.

The purpose of these guidelines is to establish concrete, evidence-based procedures for the examination/analysis/evaluation of acute ischemic stroke. In addition, our intention is to reduce the technical differences in CTP/MRP examinations between institutions and to contribute to the improvement in the prognosis of patients with acute stroke treated by thrombolytic therapy.

The guidelines were drafted by reviewing 186 of the 758 documents collected according to the procedures recommended by the Ministry of Health, Labour and Welfare of Japan. The evidence levels and recommendation grades were classified according to those employed in the Japanese Guidelines for the Management of Stroke 2004 by the Joint Committee for the Guidelines for the Management of Stroke. Although there were fields that had limited amount of publications, the opinions of the Drafting Committee members, as experts in this field, were described wherever possible. The technical details of the procedure guidelines were meant to be within the applicable range for daily clinical practice in general institutions, and we also took future multi-center clinical trials into consideration. On the other hand, while we attempted to concisely describe the relevant procedures, we maintained consistency between the present guidelines and other guidelines as well as between those of CTP and MRP. Guidelines for xenon (Xe)-CT and the arterial spin labeling technique were omitted from the present guidelines, even though they are also cerebral circulation examinations performed using CT or MRI.

The present guidelines aim to act as a point of reference for better diagnosis/treatment and are not intended to obstruct the discretion of health-care professionals or the uniqueness in developing software by the companies. Furthermore, the guidelines do not recommend the use of CTP or MRP in the evaluation of acute stroke. The Japanese Stroke Association Guidelines for Appropriate Treatment by Intravenous rt-PA (alteplase) Therapy repeatedly place much emphasis on the following point: Every effort should be made to avoid a delay in initiating drug administration due to unnecessary imaging examinations. Thus, for the time

being, these imaging examinations are considered as methods to be carefully employed in clinical research.

In these guidelines, only CTP and MRP are described; the procedure guidelines for other examination methods are still in the process of being drafted. The present guidelines are thus scheduled to be published again in the second quarter of the next year as comprehensive procedure guidelines. The authors will also employ the products of standardization of diagnostic imaging for acute stroke presently underway in Japan, as needed.

We hope that the present guidelines will complement other clinical practice guidelines and will also be used for the diagnosis, therapy, and research of acute ischemic stroke.

Classification of evidence levels

- Ia** Meta-analysis of randomized controlled trials
- Ib** Randomized controlled trials
- IIa** Well-designed (nonrandomized) controlled trials
- IIb** Well-designed quasi-experimental study
- III** Well-designed nonexperimental descriptive study
(e.g., comparative studies, correlation studies, case control studies)
- IV** Expert committee reports, opinions, and/or experience of respected authorities

(Japanese Guidelines for the Management of Stroke 2004)

Classification of recommendation grades

- A** Use is strongly recommended.
- B** Use is recommended.
- C1** Use may be considered, although there is not sufficient scientific evidence.
- C2** Use is not recommended because there is no scientific evidence.
- D** Use is not recommended.

(Japanese Guidelines for the Management of Stroke 2004)

CTP imaging

I. Examination

Recommendations

1. The tube voltage/current/rotation speed should be set as low as possible to minimize the radiation exposure to patients. **(Grade B)**
2. The imaging planes should be determined based on clinical information and noncontrast CT findings. Commonly used imaging planes include the basal ganglia and the body of the lateral ventricles. **(Grade C1)**
3. The scanning planes should be set such that direct radiation exposure to the eye lenses is avoided. **(Grade A)**
4. Nonionic contrast medium (300 to 370 mgI/dL) is generally injected into the right medial antecubital vein at a total dose of 30 to 60 mL. It is desirable to scan for 45 to 60 sec, beginning 5 sec after the initiation of the contrast injection. **(Grade B)**
5. The contrast medium should be injected at a rate of 3 to 5 mL/sec by using a mechanical injector when the deconvolution algorithm is applied for analysis. **(Grade B)**

1. Equipments

- a. Using multidetector-row CT (MDCT), it is now possible to simultaneously evaluate multiple planes in a single examination. CTP should thus be performed using MDCT rather than by using a single helical CT scanner. (IV)
- b. A mechanical injector is essential for injection of the contrast medium. (III)

2. Contrast media

- a. A nonionic, iodinated contrast medium should be used. (III)
- b. It is necessary to evaluate renal functions and the presence/absence of a history of allergy prior to the examination. (IV)
- c. The contrast medium is used at a concentration of 300 to 370 mgI/dL. Although at a lower concentration (300 mgI/dL), the contrast medium can produce a relatively satisfactory result, the administration of the contrast medium at a higher concentration may be advantageous in lowering the total injection dose, leading to better images. (III)
- d. Syringe-type preparations are now in widespread use in Japan. There are many reports of using a 100-mL syringe for the injection of the contrast medium at a higher concentration (350 to 370 mgI/dL) when CT angiography (CTA) is performed concurrently with CTP. (IV)

3. Injection doses of contrast media

- a. Adequate data on the optimal injection dose of the contrast medium is not available. (IV)

- b. The injected doses for perfusion imaging should be smaller when performing CTA concurrently or when conventional cerebral angiography is planned immediately after the CTP examination. (IV)
- c. A higher dose of the contrast medium at the same injection rate leads to a prolonged injection time, resulting in increased radiation exposure due to the longer scanning time. (III)
- d. By injecting the contrast medium at a higher concentration (350 to 370 mgI/dL), the injection dose can be reduced. (III)
- e. The total iodine dose in the contrast medium is considered to be related to the accuracy of image analysis. Thus, when a medium-concentration contrast medium is used, a higher total dose should be used than when using a high-concentration contrast medium. (III)

4. Methods of injection

- a. The optimal injection rate of the contrast medium is dependent on the analysis methods. (III)
- b. A high injection rate is not necessary for the deconvolution algorithm, and the contrast medium is generally injected at a rate of 3 to 5 mL/sec. According to some reports, it is possible to inject the medium even at a rate of 1.5 mL/sec [1, 2]. (III)
- c. It is considered that an injection rate of 9 mL/sec or higher is necessary for the maximum slope algorithm [3, 4], although there are reports that indicate that an injection rate of 5 to 6 mL/sec is also feasible. (IV)
- d. It is recommended that the right medial antecubital vein be secured for the insertion of an indwelling needle with a minimum diameter of 20 G. Injection from the left antecubital vein may cause the reflux of the contrast medium to the internal jugular vein. A longer distance to the heart may also degrade the bolus quality of the contrast medium. (IV)
- e. It is also possible to “push” the contrast medium with physiological saline; however, this is not commonly practiced in emergency examinations because it may complicate the procedure. (IV)

5. Methods of scanning

A. Scanning range

- a. The scanning range and the number of scanning planes are highly dependent on the CT devices used. Generally, 2 to 4 planes covering a range of 20 to 40 mm are imaged when MDCT is used. (III)
- b. The whole brain should be examined by noncontrast CT prior to performing CTP. The scanning planes for CTP should be decided in conjunction with the noncontrast CT findings as well as the clinical information. (III)
- c. One can select the scanning planes at any desired location of the brain, although planes that include the basal ganglia and the body of the lateral ventricles are generally selected. (III)
- d. The scanning planes should be set superior to the orbits to avoid radiation exposure to the lenses. (IV)
- e. CTP of the posterior cranial fossa has been reported [5], but in this case, the CT gantry should be tilted to avoid radiation exposure to the lenses. (IV)

B. Scanning time

- a. It is common to scan for 45 to 60 sec, beginning from 5 sec after the initiation of the contrast medium injection; however, sufficient data to determine the optimal scanning duration is not available. (IV)
- b. It is recommended that the tube rotation speed be set at as low as possible (1.5 to 2 sec) to minimize the radiation exposure to patients. It is also desirable to set the image reconstruction interval at 1 image/sec. (IV)
- c. When real-time monitoring during scanning is feasible, one can attempt to reduce the radiation exposure by discontinuing scanning upon completion of the first pass of the contrast medium. (IIb)
- d. With some scanners it is possible to reduce radiation exposure by intermittent scanning. A scanning cycle of “1 second on-1 second off” has been shown to be sufficient to preserve the quantitative results [6]. (IIb)

C. Scanning conditions

- a. The radiation exposure in CTP is in general greater than that in noncontrast head CT. (III)
- b. The local radiation dose should be evaluated by $CTDI_{vol}$ ($CTDI_w \times$ number of rotations)*. (IV)
- c. The tube current should be set as low as possible to reduce the radiation exposure, but there is insufficient data to determine the optimal current to be used. (IV)
- d. The tube voltage should be set as low as possible (80 to 100 kVp) to reduce the radiation exposure and augment the imaging contrast [7]. (III)
- e. An excessively lowered radiation dose may cause increased noise in the images and may alter the quantitative values. It is thus necessary to determine appropriate scan parameters for each device. (IV)

D. Repeated scanning

- a. The maximum permitted dose of the contrast medium for head CT in Japan is 100 mL. It is thus feasible to repeat examinations 2 to 3 times by using an injection dose of 30 mL. (IV)
- b. When repeated examinations are to be performed, it is recommended to perform imaging slabs at intervals of 5 to 10 mm to avoid overlapped radiation exposure. (IV)

6. Concurrent use with CT angiography

- a. The successive performance of noncontrast CT, CTP, and CTA has been reported to be safe [8]. When performing these modalities on children, the elderly, and subjects with a low body weight, however, one may need to pay close attention to the total radiation exposure as well as to the total dose of the contrast medium. (IV)
- b. The concurrent use with CTA frequently provides clinically useful information on the vascular state such as the presence of occlusion sites and the degree of stenosis. (IV)
- c. When CTA is performed prior to CTP, it may cause inaccurate estimation of CTP results, although this effect depends on the analysis used. It is thus common practice to perform CTP 2 to 3 min prior to CTA. (IV)

*CTDI_{vol} (volume computed tomography dose index): An index for the evaluation of the radiation dose in CT. The unit generally used to measure the radiation dose is mGy. CTDI_{vol} can be used in the evaluation of helical or dynamic scans of CT or MDCT by converting CTDI_w (weighted computed tomography dose index), an index of the absorbed dose per cycle, to the dose per cm.

II. Image analysis

Recommendations

1. The operator must become familiar with the analysis procedures in order to be able to promptly provide the results without delay after completion of the examination. **(Grade C1)**
2. The data should be analyzed by the deconvolution algorithm. Cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) images should be provided. **(Grade B)**
3. The details and results of the analysis differ depending on the software vendor, and a highly reliable analysis technique has not yet been established. **(Grade C2)**
4. Under the present conditions, the quantitative values obtained by CTP have poor reliability. **(Grade C2)**

1. Image analysis methods

- a. The maximum slope and deconvolution algorithms are the two major classes of analyses methods that are currently being used clinically. (IIb)
- b. The deconvolution algorithm can be used at a low injection rate of the contrast medium and is thus becoming common in Japan. (IV)

2. Analysis operation

A. Analysis flow

- a. Each vendor provides its own analysis software programs. (IV)
- b. Different software may provide different results even when the same image data set are used. Under the present conditions, analysis is generally conducted by using the software provided by the vendors. (IIb)

B. Arterial input function and venous output function

- a. There is no consensus as to the region at which the arterial input function (AIF) should be determined, and the practical selection of the location varies according to the researcher and the analysis software programs used. (IV)
- b. The region for AIF selection is frequently set at the middle or anterior cerebral artery on the unaffected hemisphere. (III)
- c. If the input function is determined in arteries other than the artery supplying the ischemic lesion, the degree of ischemia is generally overestimated [4]. (III)
- d. The venous output function influences the quantitative values but does not affect the qualitative evaluation [9, 10]. (IIb)

C. Vascular-pixel elimination

- a. Vascular-pixel elimination methods differ depending on the software used, and standard techniques have not yet been established. (IV)

- b. The presence/absence of vascular-pixel elimination causes large differences in the apparent analysis results and the measured values [11]. (IIb)
- c. Optimization of the vascular-pixel elimination method leads to a higher correlation with other cerebral blood flow examinations [11]. (IIb)

3. Displaying the analysis results

- a. Color maps are commonly used to display images of the following three parameters: CBF, CBV, and MTT. The time-to-peak (TTP) map is also available in some software. (III)
- b. As for the number of pixels, 256 or 128 matrices are generally employed from the viewpoint of noise control, but it is now also possible to analyze the data using 512 matrices. (III)
- c. With regard to the display of color maps, the respective vendors or users provide their own settings of the color tone (look up table: LUT), scale, etc., resulting in considerable differences in image appearance between institutions. (III) The establishment of a standard display method will be necessary in the future. (IV)

4. Reliability of quantitative values

- a. Some studies have been conducted using quantitative values [12], but these values are highly dependent on the scanners or analysis software programs used. It is thus necessary to pay adequate attention to the fact that these results cannot be generalized. (IV)
- b. Semi-quantitative evaluation (using the ratio between the affected and unaffected hemisphere) is a promising method compared with quantitative evaluation. (III)
- c. According to some of the recent reports [12-15], an area showing a 30%–40% decrease in CBF compared to the unaffected side is an ischemic lesion that can be salvaged, and an area showing a CBF decrease of 70%–80% or more will eventually become infarcted. Sufficient evidence, however, is not available on the reliability of such semi-quantitative values. (IV)

III. Image evaluation

Recommendations

1. The area of perfusion deficit is determined by MTT images. **(Grade B)**
2. The severity of ischemia may be estimated from the ratio of the CBF between the affected and unaffected hemispheres. **(Grade C1)**
3. No CTP criteria have been established for the indication for thrombolytic therapy. **(Grade C1)**

1. Methods of evaluation

- a. Three types of color maps (CBF, CBV, and MTT) are commonly prepared for the qualitative evaluation of the extent and severity of ischemia. (III)
- b. Quantitative or semi-quantitative values (affected to unaffected side ratios) are frequently used, but their reliability has not yet been proven. (III)
- c. Quantitative or semi-quantitative values cannot be directly compared between patients or examinations, except in cases in which the data acquisitions are carried out by using the same scanner and the same analysis method. (IV)
- d. No CTP criteria have been established to judge the indication for thrombolytic therapy. (III)

2. Clinical significance

- a. In comparison with other methods of perfusion studies (Xe-CT, single-photon emission computed-tomography (SPECT)), CTP examines the perfusion deficit of the brain within the shortest period of time [8, 16]. (III)
- b. A combination of noncontrast CT, CTP, and CTA using MDCT has been shown to be advantageous, when compared with each examination performed alone. Combined study was shown to increase the sensitivity of detecting lesions, predicting the final infarct size, and the diagnosis of clinical types of infarctions (cardiogenic embolism, atherothrombotic infarction, or lacunar infarction) [4, 17-19]. (III)
- c. It is possible to detect the perfusion deficit area by CTP before noncontrast CT reveals early ischemic changes [20, 21]. (III)
- d. The size of the perfusion deficit determined by CTP correlates with the prognosis of patients [22,23]. (III)
- e. CTP is limited in its cover range, making it impossible to judge perfusion deficit outside the scan range [20, 24, 25]. (III)
- f. It is often difficult for CTP to detect small ischemic lesions, including lacunar infarctions [17, 26-29]. (III)
- g. MTT is the most sensitive in depicting perfusion deficit [12], along with TTP, which is also very sensitive [20, 26]. The perfusion deficit area as measured by both MTT and TTP, however, is greater as compared with the final infarct size. [13] (III)
- h. An increase in CBV reflects the collateral pathway or autoregulation and a decrease in CBV indicates an unfavorable state [30]. (III) The significance of CBV in prognosis prediction differs from study to study [12, 31, 32]. (III)
- i. A decrease in CBF is a highly sensitive as well as specific finding in predicting an

infarction [13]. It also correlates well with the size of the final infarction lesion [17]. (III)

3. Comparison with other modalities

- a. CTP results have been shown to correlate well with those obtained by MRP [33, 34]. (III) In addition, the decreased CBV area in CTP has been found to be in good agreement with the DWI high-signal area [4, 33, 35] and correlates well with the volume of the final infarction lesion [34]. (III)
- b. It has been reported that CTP results are almost comparable with those of diffusion-perfusion mismatch (DPM) in estimating the penumbra [45]. (III)
- c. The results obtained using CTP have been shown to correlate well with the results of Xe-CT [3, 36, 37]. Semi-quantitative values (affected to unaffected side ratios) show a higher correlation than the quantitative values. (III) It has been also reported that CBF measured by CTP in severe cases may show extremely higher values when compared to those by Xe-CT [38]. (III)
- d. CTP data correlate well with those of single-photon emission computed-tomography (SPECT) [39]. The quantitative CBF values obtained using the former modality, however, are rather high compared with those obtained with the latter [40], and tend to be particularly high in the basal ganglia and the thalamus [40]. (III)
- e. CBF as assessed by CTP shows a favorable correlation with the values obtained using $H_2^{15}O$ positron emission tomography (PET), if the threshold of vascular-pixel elimination is appropriately set by using the CBV map [11, 40]. (III)

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MRP imaging

I. Examination

Recommendations

1. The MR unit should have echo-planar imaging (EPI) capability and a minimum field strength of 1.5 T. **(Grade C1)**
2. The imaging volume should ideally cover the whole brain. When such an imaging volume is difficult to achieve owing to the capability of the MR unit, the imaging volume should at least include the inferior margin of the basal ganglia and also the superior margin of the lateral ventricle. **(Grade C1)**
3. A gadolinium-based contrast medium is generally injected from the right medial antecubital vein at a total dose of 0.1 mmol/kg and at a rate of 5 mL/sec by using a mechanical injector. The subsequent injection of 20 mL of physiological saline (at 5 mL/sec) will facilitate a more effective delivery of the bolus of the contrast agent **(Grade B)**
4. Data acquisition by gradient-echo echo-planar imaging (GRE-EPI) is more common. **(Grade C1)**
5. Data acquisition should begin before the injection of the contrast medium. **(Grade C1)**

1. Equipments

- a. There are almost no reports describing the use of MRP for evaluating stroke at a low magnetic field (0.5 T or below) or even at a medium magnetic field (1.0 T). In addition, the quality of the perfusion image may not be secured at low/medium field strength, and thus examination with a 1.5-T device is recommended. **(III)**
- b. A previous study reported perfusion imaging performed using a conventional GRE sequence. This method, however, can only image a single plane. It will also be impossible to obtain DWI in a short period of time by using these old MR units. It is thus recommended that devices that are capable of echo-planar imaging (EPI) be used. **(III)**
- c. A mechanical injector should be used for the injection of the contrast medium in order to maintain constant injection conditions. **(IV)**

2. Injection doses of contrast media and methods of injection

- a. A gadolinium contrast medium should be used.
- b. The standard dose of the contrast medium is 0.1 mmol/kg. It is acceptable, however, to inject the full contents of a syringe containing the contrast medium since many contrast media are now available as syringe-type preparations. **(IV)**
- c. In order to attain a high bolus quality of the contrast medium, it is desirable to secure the right antecubital vein with an indwelling needle with a minimum diameter of 20 G. When it is difficult to secure such a route in the same site, the left antecubital vein may be secured by using a 22-G needle [1]. **(IV)**

- d. It is desirable to inject the medium at a rate of 5 mL/sec, but it is also possible to analyze the data at a rate of approximately 3 mL/sec if the injection route or the blood vessel is thin/fragile. Sufficient evidence for performing perfusion imaging by injecting the contrast medium at a slow rate is not available [2]. (III)
- e. Even when there is a venous route secured in advance, it is desirable to obtain another suitable route for the injection of the contrast medium. (The medium is injected at a high rate; therefore, it is necessary to pay attention to the pressure proof quality and size of the route.) (IV)

3. Methods of data acquisition

A. Imaging range

- a. In cases of acute cerebral infarction, the imaging range should be decided with reference to the DWI findings and clinical symptoms. (IV)
- b. It is desirable to scan the whole brain. If the imaging range is limited, however, it may be set to include the area from the inferior margin of the basal ganglia to the superior margin of the lateral ventricles. (IV)
- c. When a lesion is suspected at the posterior fossa based on the clinical symptoms, etc., the imaging range should be lowered to include the cerebellum/brain stem; however, there is insufficient evidence available for the usefulness of perfusion imaging for the evaluation of the posterior circulatory system. (IV)

B. Imaging parameters

- a. The imaging parameters strongly depend on the MR equipment being used and thus the optimal parameters for each MR unit should be selected. The standard imaging parameters are shown below. (IV)
 - 1) Sequence: GRE-EPI
 - 2) Repetition time (TR): 1500 msec (1000 to 2000 msec)
 - 3) Echo time (TE): 60 msec (50 to 80 msec)
 - 4) Slice thickness: 6 mm (5 to 10 mm)
 - 5) FOV: 24 × 24 cm (20 × 20 cm to 40 × 20 cm)
 - 6) Matrix: 128 × 128 (64 × 64 to 128 × 64)
 - 7) Number of images obtained: 10 (5 to 20)
 - 8) Scanning time: Set so as to perform continuous scanning for 60 to 90 sec
- b. Parallel imaging (sensitivity encoding (SENSE), array spatial sensitivity encoding technique (ASSET), simultaneous acquisition of spatial harmonics (SMASH), SPEEDER, etc.) should be combined if possible (such a combination will lead to reduced artifacts or an increased number of images obtained) [3]. (III)
- c. GRE-EPI may be recommended since a decrease in the signal by the passage of the contrast medium is larger in GRE-EPI when compared with spin-echo EPI (SE-EPI), and that the signal-to-noise ratio (SNR) is high in perfusion imaging. SE-EPI is considered to reflect to a greater extent the perfusion in the cerebral parenchyma whereas GRE-EPI is strongly influenced by large blood vessels [4–7]. (III)
- d. It is desirable to scan at intervals (TR) of 2 sec or less [8]. (III)
- e. The signal intensity is unstable in several images immediately after the start of data acquisition. It is thus desirable to begin scanning before the injection of the contrast medium (approximately 5 sec before the start of injection) in order to

- stabilize the baseline image before the arrival of the medium [8]. (III)
- f. The first pass of the contrast medium is generally completed 40 to 50 sec after the initiation of injection, but it is desirable to scan for 60 to 90 sec since the cerebral circulation is slow in some cases. (IV)

II. Image analysis

Recommendations

1. An environment that enables prompt data analysis and the display of results immediately after the completion of the examinations is required. **(Grade C1)**
2. The first-moment algorithm is one of the most commonly used techniques and may be adequate in computing the MTT. **(Grade C1)**
3. The results of data analysis may differ depending on the software used, and a standardized highly reliable technique for analysis has not yet been established. **(Grade C2)**
4. At present, the quantitative estimation of perfusion parameters is generally not carried out in MRP imaging. **(Grade C2)**

1. Image analysis methods

- a. Qualitative values of CBV are computed from the area under the time-signal intensity curve [9, 10]. (Iib) The calculation of CBV is extremely straightforward and is influenced to a very small extent by the post-processing software. (III)
- b. One of the most commonly used methods for calculating MTT includes the first-moment algorithm or the deconvolution method. The first-moment method involves a simpler computation technique and a shorter post-processing time compared with the deconvolution algorithm. The deconvolution algorithm is, however, advantageous in providing a more exact estimation of MTT, although it requires selection of the arterial input function and a more complicated computation [11, 12]. (Iib)
- c. TTP represents the time taken for the time-concentration curve to reach the peak. It may be used instead of MTT because the computation is simpler.
- d. The quantitative values of CBF may be obtained by using the deconvolution algorithm [13, 14], although it is uncommon for such values to be used in the acute phase of ischemic stroke. (III)
- e. In MRI, it is known that the correlation between the blood concentrations of the contrast medium and the signal change as measured on the MR image is not perfectly linear. It is thus known that quantitative values may be difficult to obtain in MRP compared with CTP [15, 16]. (Iib)

2. Image analysis operation

- a. At the acute phase of a cerebral infarction, it is important to analyze the data without delay after the completion of the examination. (IV)
- b. At present, no MRI vendors provide deconvolution analysis software programs that can be used on the MRI console for routine examinations. (IV)
- c. A consensus has not yet been reached on the location at which the arterial input function should be measured for the deconvolution method, and the strategies differ depending on the researcher or the analysis software program used [17]. (III)
- d. The arterial input function is often measured from the internal carotid artery or the middle cerebral artery (MCA) on either the unaffected or affected sides. A change in

the setting of the arterial input function, however, may cause substantial changes in analysis results, and thus needs careful consideration [18]. (III)

3. Displaying the analysis results

- a. Perfusion parameters, such as MTT and TTP, are displayed either in color or gray scale maps. (IV)
- b. The areas of perfusion deficits are generally most conspicuous when measured using transit-time parameters, including MTT and TTP, as compared with using CBF and CBV. (IV)
- c. Each MRI vendor uses its own scheme for color map display (look up table: LUT) and window settings, resulting in substantial differences in image appearance. A standardized display method needs to be established in the future. (IV)

III. Image evaluation

Recommendations

1. The perfusion deficit area is most adequately assessed by using MTT. **(Grade B)**
2. The diffusion-perfusion mismatch (DPM) area is estimated by comparing the results of MTT images with hyperintense lesion depicted by DWI. **(Grade C1)**
3. Thrombolytic therapy is indicated for those cases with DPM, but the criteria for inclusion have not yet been established. **(Grade C1)**

1. Methods of evaluation

- a. The areas with a prolonged MTT will be defined as regions with a perfusion deficit. Within these areas, regions without high-intensity on DWI will be judged to be areas with DPM [19, 20]. (III)
- b. There are some reports that have assessed the degree of MTT (or TTP) prolongation by thresholding the delay by 2-sec increments [21–23]. (III)
- c. DPM as assessed by a single rater is known to show relatively high reproducibility. Interobserver agreement between different raters is, however, known to be low. This indicates that the establishment of a standardized method of evaluation will be required in the future [24]. (III)

2. Clinical significance

A. Detection of ischemia in acute stroke

- a. From the onset of symptoms, it is possible to detect the hypoperfused region by perfusion imaging in the early stages of ischemia [25]. (III)
- b. The penumbra (functionally impaired but structurally intact ischemia, which may escape from infarction by reperfusion but may result in infarction if the blood flow does not resume) is expected to be situated within the DPM area [26]. (III)
- c. DPM of various degrees can be recognized in many cases of cerebral infarction in the early stages of ischemia (within 24 hrs) [25, 27, 28]. (III)

B. For which cases should MRP imaging be used?

- a. MRP imaging is generally used for the evaluation of the anterior circulation system (regions supplied by the internal carotid artery, anterior cerebral artery, and MCA) and also the posterior cerebral artery territory. (III)
- b. MRP imaging is not generally used for evaluating the perforating artery territory or the brain stem. This is because the technique is limited in spatial resolution and also because of magnetic susceptibility artifacts that may make the interpretation of the images very difficult [29]. (III)
- c. A major branch occlusion may be suggested by the intra-arterial hyperintensity on fluid-attenuated inversion-recovery (FLAIR) images or by the susceptibility sign at the proximal MCA on T2*-weighted images. These signs may sometimes help to determine the indication for perfusion imaging [30, 31]. (III)

- d. There is to date no concrete evidence indicating the clinical or socioeconomic benefit of using MRP for patients with acute ischemic stroke. (III)

C. Perfusion parameters and their clinical significance

- a. In cases of acute ischemia, the transit time (MTT or TTP) is prolonged, and generally, areas with such a prolongation of the transit time are found over a wider range when compared with areas that show a deficit in the CBV or CBF [28].
- b. It has been reported that the area showing a marked prolongation of the transit time (MTT or TTP) (prolongation of 4 sec or more) undergoes irreversible infarction [23, 32]. (III)
- c. The area showing reduced CBF will have a high likelihood of undergoing infarction. The threshold for determining the CBF abnormality, however, differs from report to report, and it will be difficult to set a unified standard [27, 28, 32]. (III)
- d. An increase in CBV is caused by the compensation of circulatory reserve capacity (reactive dilatation of capillary vessels and collateral circulation). A decrease in the CBV is caused by a decrease in perfusion pressure beyond the limits of reserve capacity [25, 33]. (III)
- e. It has been reported that the area showing a marked reduction in CBV undergoes infarction, but it is again difficult to set a clear-cut threshold [34, 35]. (III)

D. Deciding the indication for thrombolytic therapy using MRP imaging

- a. DPM has thus far been used as part of the inclusion criteria in only one clinical trial of thrombolytic therapy (i.e., the Desmoteplase in Acute Ischemic Stroke Trial: DIAS). A practical or standardized criterion has not yet been established that defines the degree of DPM for the indication of thrombolytic therapy [36]. (Ib)
- b. MRP imaging has been commonly used for planning treatment regimens in many leading institutes [37], and their decision-making criteria have been published. These are, however, not based on scientific evidence. The establishment of standardized criteria for decision-making will be necessary in the future. (IV)

For reference, the criteria for patient selection by MRI in DIAS [36] are shown later (Appendix 4).

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Reviews and textbooks

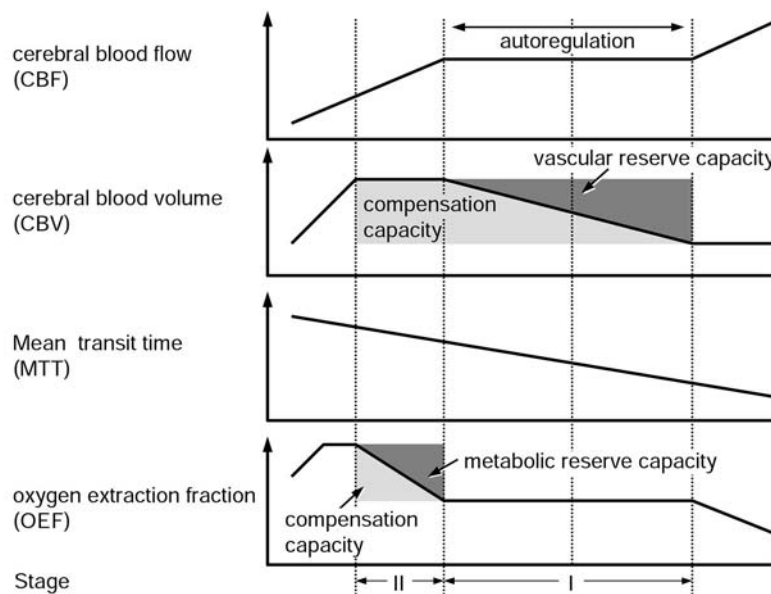
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Appendix 1. Cerebral hemodynamic ischemia and parameters for perfusion imaging

MTT, CBV, CBF, and TTP are the representative parameters derived from perfusion imaging. The relationship between these parameters and the pathophysiology of brain circulation and metabolism will be addressed along with cerebral hemodynamic ischemia.

The stenosis or occlusion of a cerebral artery causes a compromise in perfusion pressure; this is followed by the immediate dilatation of the cerebral capillaries by the autoregulation system. This dilatation causes an increased regional CBV, resulting in the maintenance of regional CBF. MTT is prolonged at this stage (Stage I). If the perfusion pressure is lowered beyond the limits of the vascular reserve capacity, the oxygen supply is compensated by increasing the oxygen extraction fraction (OEF) (Stage II). It is unfortunately not possible, at the moment, to directly measure the OEF by using MRP imaging.

If the perfusion pressure is further lowered, the oxygen supply cannot be completely compensated, not even by the increase in the OEF, and the tissue may become infarcted. The area with a decreased CBV is in a state of capillary collapse, and the infarction is considered to be irreversible. (Modified from "Powers et al. Ann Neurol, 16:546–552, 1984")

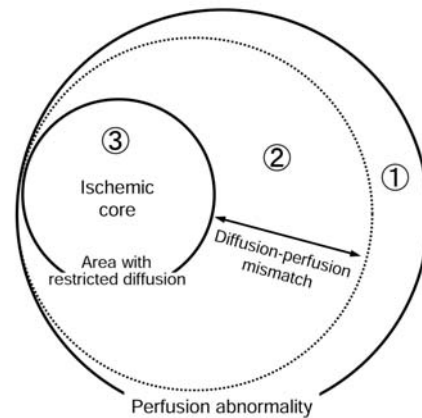


Appendix 2. DPM (diffusion-perfusion mismatch)

At the acute phase of a large territorial cerebral ischemia, there may be a central core area with irreversible changes surrounded by an area of hypoperfusion. The penumbra, in general, points to the hypoperfused area surrounding the core that may be salvageable by reperfusion. There is to date, however, no consensus as to which parameter should be used to evaluate the penumbra.

The DPM area will have time-course changes, and the core area (infarction) will increase over time, resulting in a reduction in the DPM area.

- ① Area with a prolonged TTP
- ② Area with a prolonged MTT
Increased or slightly decreased CBV
Slightly decreased CBF
- ③ Ischemic core (= infarction)
 - Decreased apparent diffusion coefficient (ADC)
 - Markedly decreased CBF and CBV



DPM (MTT-DWI mismatch): ②–③)
(Recommended in the present guidelines)

Appendix 3. Outline of perfusion imaging

In the contrast perfusion imaging technique, an iodinated contrast medium and a gadolinium contrast medium are intravenously injected for CT and MRI, respectively. Dynamic imaging is performed over time to acquire time-concentration curves of the brain tissue. Various perfusion parameters are calculated using these curves.

In CT, the level of the iodinated contrast medium in the cerebral parenchyma or in blood vessels increases in proportion to the concentration of the medium.

The contrast medium concentration in the cerebral tissue $[C_t(t)]$ may be expressed by convolution of the arterial input concentration $[C_a(t)]$ and the transfer function $[h(t)]$.

$$C_t(t) = C_a(t) * h(t) = \int C_a(t-s)h(s)ds$$

Changes in the CT values of the cerebral parenchyma $[C_t(t)]$ and of the artery $[C_a(t)]$ are measured from the CT data over time and then the results are subjected to deconvolution to obtain $h(t)$ values. The MTT of the contrast medium in the tissue is obtained from the following equation.

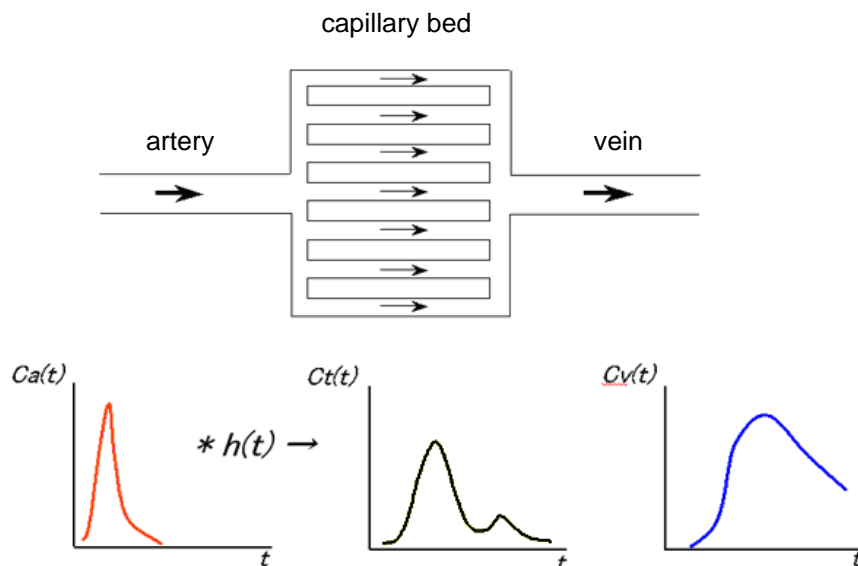
$$MTT = \int h(t)tdt / \int h(t)dt$$

On the other hand, the volume of the contrast medium in tissues, the CBV, is in proportion to the area under the curve (AUC) of the curve $C_t(t)$. Thus, the quantitative value of CBV is obtained by correcting the result by the AUC for the output route (vein).

$$CBV = \int C_t(t)dt / \int C_v(t)dt$$

Using the MTT and CBV values obtained, the CBF is calculated using the central volume principle as follows.

$$CBF = CBV / MTT$$



As for MRI, the gadolinium contrast medium is a paramagnetic material, and thus has a susceptibility effect due to its difference in magnetic susceptibility from the surrounding tissues while it passes through the vessel. This effect causes a lowered signal intensity in T2-weighted imaging or T2*-weighted imaging.

The relationship between the concentration of the contrast medium and the signal intensity in voxels at time t is generally expressed by the following equation.

$$C(t) = k\Delta R2^* = -k\ln[S(t)/S(0)]/TE$$

C(t): Concentration of contrast medium at time t

$\Delta R2^*$: Change in T2* relaxation rate ($=1/T2^*$) before and after imaging

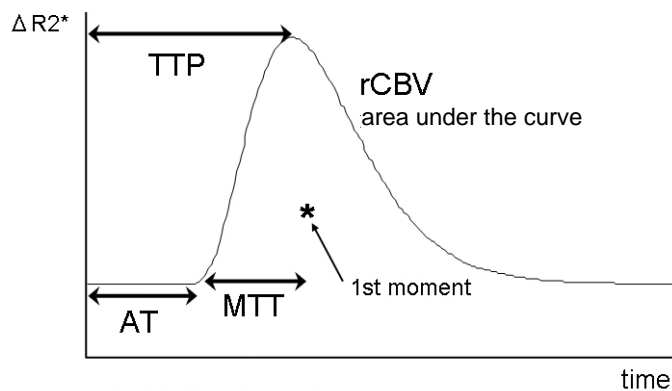
S(t): Signal intensity at time t

TE: Echo time

k = Constant

In MRP, the TTP of the contrast medium and the MTT determined by the first-moment algorithm are calculated from the time-concentration curve (Figure).

In MRP, similar to CTP, the various parameters, including CBF, CBV, and MTT, are calculated quantitatively using the deconvolution algorithm. It is difficult, however, to obtain an absolute value of the constant K, because this constant depends on the tissue, contrast medium, magnetic field strength, and imaging sequence.



TTP: time to peak
 MTT: mean transit time
 AT: arrival time

Appendix 4. MRI diagnostic criteria in DIAS

(Adapted from the paper by Hacke W, et al. Desmoteplase in Acute Ischemic Stroke Trial (DIAS): a phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. Stroke 2005; 36:66–73)

Inclusion criteria

- Presence of PWI/DWI mismatch of at least 20% (by visual evaluation)*
- Abnormality extending to the cortex of the hemisphere

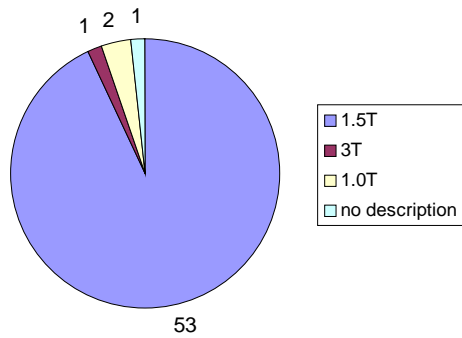
* The perfusion imaging was evaluated by either TTP or MTT (not based on standardized method/criteria).

Exclusion criteria

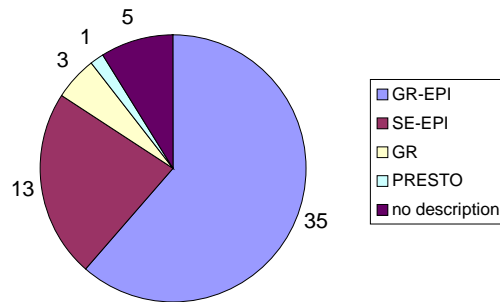
- Evidence of intracranial hemorrhage (ICH)
- Evidence of subarachnoid hemorrhage (SAH)
- DWI abnormality involving over 1/3 of MCA territory
- No perfusion deficit
- Internal carotid artery occlusion ipsilateral to the stroke lesion without additional ipsilateral middle, anterior, or posterior cerebral artery occlusion
- Any intracranial pathology interfering with the assessment of diffusion and perfusion abnormalities
- Contraindications to MRI

Appendix 5. Summary of MRP scanning and analysis methods in 57 institutions

Magnetic field strength



Imaging sequence



Scanning parameters

- TR in EPI: 260–3300 msec, 1500–2000 msec in 34/47 (72%)
- TE: varies in the range of 25 to 70 msec in GRE-EPI and 42 to 120 msec in SE-EPI
- Number of slices: 5–19, 8–12 in 27/38 (71%)
- Slice thickness: 5–10 mm, 5–6 mm in many cases

Injection doses of contrast medium

0.05 mmol/kg	1
0.1 mmol/kg	20
0.15 mmol/kg	1
0.2 mmol/kg	18
15 mL	5
20 mL	5
30 mL	2
no description	5

Injection rate of contrast medium

2 mL/s	1
4 mL/s	3
5 mL/s	26
>7 mL/s	5
manual injection	4
no description	18

Analysis algorithms

