Fully Automated and Real-Time Volumetric Measurement of Infarct Core and Penumbra in Diffusion- and Perfusion-Weighted MRI of Patients with Hyper-Acute Stroke

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Abstract

Multimodal magnetic resonance imaging (MRI) has emerged as a promising tool for diagnosing ischemic stroke and for determining treatment strategies in the acute phase. The detection and quantification of the penumbra and the infarct core regions aid the assessment of the potential risks and benefits of thrombolysis by providing information on salvageable tissue or ischemic lesion age. In this study, we proposed a fully automated and real-time algorithm to compute parameter maps of perfusion-weighted images (PWIs) and to identify an infarct core from diffusion-weighted images (DWIs). DWI and PWI were obtained using a 1.5 Tesla MRI scanner for 15 patients with acute ischemic stroke. Parameter maps of PWI were computed using restricted gamma-variate curve fitting and Fourier-based deconvolution. The ischemic penumbra was identified using time-to-maximum ($T_{\max}$) > 6 s as the mutual optimal threshold, while the infarct core was segmented using an adaptive thresholding on DWI. When the penumbra on PWI was compared with that generated using commercial software Pearson's linear correlation coefficient between penumbra volumes was 0.601 ($p = 0.030$), and the Dice coefficient was 0.51 ± 0.15 . The infarct core on DWI was compared with the manually segmented gold standard. Dice coefficient between the manually drawn and automated segmented infarct cores was 0.62 ± 0.18 . The processing times for PWI and DWI were 222.9 ± 16.4 and 53.4 ± 4.8 s, respectively. In conclusion, we demonstrate a fully automated and real-time algorithm to segment the penumbra and the infarct core regions based on PWI and DWI.

Keywords Stroke · Penumbra · Infarct · PWI · DWI · Segmentation

Introduction

Stroke is one of the leading causes of death and long-term disabilities across the world. About 795,000 people

experience a new or recurrent stroke each year in the USA [1]. In 2013, the global prevalence of stroke was 25.7 million, and there were 6.5 million stroke deaths worldwide, making stroke the second-leading cause of death behind ischemic heart disease [1]. For the last few decades, improving the treatment outcome of acute ischemic stroke has become a subject of great challenge. The treatment options highly depend on the time window [2, 3]. Intravenous recombinant tissue plasminogen activator (rt-PA) is available up to 4.5 h from symptom onset [2, 4, 5], whereas intra-arterial mechanical thrombectomy has demonstrated a clear benefit up to 6 h [6–9]. Recent clinical trials including EXTEND-IA [10], ESCAPE [11], SWIFT PRIME [12], MR CLEAN [13], DAWN [14], and DEFUSE 3 [15] have demonstrated the promise of endovascular therapies, but the selection of patients who may benefit from reperfusion therapy is still one of the most critical tasks in acute stroke care.

Multimodal magnetic resonance imaging (MRI) has emerged as a promising tool for diagnosing ischemic stroke and for determining treatment strategies in the acute phase.

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Various imaging findings from MRI sequences could reflect a snapshot of the stroke state of the brain tissue at a point in time. Thus, MRI can be used to determine eligibility for reperfusion therapies and quantification of possible benefits by identifying at-risk but viable tissue as well as ischemic tissue. The penumbra is regarded as the target tissue for reperfusion therapies; it is considered viable but at risk of becoming irreversibly infarcted [16, 17]. The penumbra, the area surrounding an ischemic lesion, is at risk of progressing to infarction but is still salvageable if reperfused. Without reperfusion, brain cells in the penumbra area would become part of the infarct lesion. The availability of MRI in clinical practice permits estimation of the infarct core and the extent of penumbral tissue. The volume of the infarct core can be derived from a diffusion-weighted image (DWI), while the volume of the penumbra around the core can be estimated using the cerebral blood profile from a perfusion-weighted image (PWI). Thus, PWI-DWI mismatch (i.e., the ratio of the sizes of the reversible penumbra to the irreversible infarct core) on MRI helps us to assess potential risks and benefits thrombolysis by providing information on salvageable tissue or ischemic lesion age [18–20].

To do this, it is necessary to detect and quantify the penumbra and the infarct core regions. However, manual segmentation of these infarct core and penumbra regions is expensive in terms of time and human expertise. Several previous studies have proposed ways to assist clinicians with this problem [21–26]. Most of these algorithms are based on multimodal MRI including PWI, DWI, apparent diffusion coefficient (ADC), T1-weighted, T2-weighted, and fluid attenuation inversion recovery (FLAIR) to provide rich information about lesions [23, 24]. A recent lesion segmentation algorithm was only based on DWI and was semi-automated [26]. Human experts mark bounding boxes around the target lesions to initialize the algorithm. Another recent lesion segmentation algorithm was fully automated, but it required a set of normal images to use as a standard reference [25]; besides, the algorithm was only applied to lesions in the occipital lobe.

In this study, we proposed a fully automated and real-time algorithm to segment the penumbra and the infarct core regions based on PWI and DWI, respectively. Our algorithm is designed to be used clinically in real-time in the emergency room and to require only images from routine clinical practice without the interaction of physician specialists.

Patients and Methods

Patients

Fifteen datasets of patients with an acute ischemic stroke were retrospectively selected and analyzed in this study (age, 52.27 ± 16.36 years; male, 8; imaging time after onset, $1.79 \pm$

1.29 h) (Table 1). The selection criterion was a sufficient image quality without movement artifacts so that biased results due to suboptimal image quality could be neglected. Moreover, only patients with a single infarction of an acute ischemic stroke within 6 h were included. The study was approved by the local institutional review board. Due to the retrospective nature of the study, written informed consent was waived.

MRI Acquisition

All MR imaging measurements were performed on a Siemens 1.5 T scanner (Siemens Avanto 1.5 T, Erlangen, Germany). DWI was obtained with the following parameters: EPI sequence; slice thickness, 5 mm; repetition time (TR), 3000 ms; echo time (TE), 86 ms; number of averages, 6; spacing between slices, 7 mm; flip angle, 90° ; pixel spacing, $0.65 \times 0.65 \text{ mm}^2$; matrix size, 384×384 . PWI was also obtained with the following parameters: EPI sequence; slice thickness, 5 mm; TR, 1390 ms; TE, 27; number of averages, 1; spacing between slices, 7 mm; flip angle, 90° ; number of phases, 40; time per phase, 1.39 s; pixel spacing, $1.95 \times 1.95 \text{ mm}^2$; pixel dimensions, 128×128 .

Perfusion Parameter Estimation on PWI

PWI was used to estimate the time-to-peak (TTP), cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT), and time-to-maximum ($T_{\max}$) map. $T_{\max}$ represents the delayed time of a bolus-shape-independent signal generated using deconvolution from a major feeding artery,

Table 1 Demographic characteristics of the acute ischemic stroke patients

No.	Age (year)	Sex	Imaging time after onset (minute)
1	37	F	75
2	79	F	126
3	65	F	147
4	27	M	146
5	68	M	134
6	67	M	37
7	56	M	7
8	60	F	58
9	44	M	143
10	85	F	327
11	66	F	151
12	64	M	27
13	68	M	55
14	36	M	106
15	67	F	75

such as the middle cerebral artery (MCA). The flowchart for the perfusion parameter estimation on PWI is shown (Fig. 1a). Each PWI scan was preprocessed as follows: time alignment, inhomogeneous field correction, head motion correction, and tissue segmentation for brain extraction. To extract the time-intensity signal, frequency bands greater than 0.1 Hz were removed using a discrete Fourier-transform (Fig. 2a). Next, a relative concentration-time curve (rCTC) was calculated as

$$rCTC(t) = -\frac{1}{TE} \ln \frac{S(t)}{S_0} \quad (1)$$

where TE is the echo time, $S(t)$ is the low-pass filtered time series, and S_0 is the average of spontaneous intensities prior to the first bolus (Fig. 2b) [27]. The gamma-variate function was used to estimate the cerebrovascular parameters for rCTC. The gamma-variate function can be expressed as

$$g(t) = \begin{cases} A(t-t_0)^\alpha \exp\left(-\frac{t-t_0}{\beta}\right), & \text{if } t > t_0 \\ 0, & \text{otherwise} \end{cases} \quad (2)$$

where t_0 is bolus arrival time (BAT) and A , α , and β are the parameters used to shape a gamma-variate function.

Using these parameters, the steepest slope and amplitude of the gamma-variate function could be acquired without any additional signal processes. Initially, BAT was determined by computing the intersection between the steepest slope line and the baseline of the time-intensity signal. Then, TTP was identified by searching for the time at the minimum intensity signal. To reduce processing time and improve the accuracy of the gamma-variate fitting, we determined these parameters (i.e., A , α , and β) using a restricted curve-fitting scheme. Without restricting the range of the parameters, the gamma-variate function can be fitted as a monotonically decreasing function. Notably, when the concentration-time curve has a sharp peak, the gamma-variate curve can be easily fitted as a monotonic function. Additionally, because the peak of the concentration-time curve is important for computing the parameter maps, the coefficients α and β were restricted as

$$TTP = \alpha\beta \quad (3)$$

Equation (3) was derived from the first differential equation of the gamma-variate function at $t_0 = 0$; i.e., the origin of the

Fig. 1 An overview of the schemes used for MRI processing in this study. **a** Flowchart for the perfusion parameter estimation on PWI. **b** Flowchart for the infarct core segmentation on DWI

Fig. 2 Time-intensity signal of PWI. **a** Raw and low-pass filtered time series. **b** Relative concentration-time curve

gamma-variate function was translated to BAT. Using the second differential equation, the inflection on the up-slope of the gamma-variate function can be determined as

$$t_{in} = (\alpha - \sqrt{\alpha})\beta \quad (4)$$

The coefficients A , α , and β can be determined by minimizing the root-mean-squared error by adjusting inflection times based on the conditions of Eqs. (3) and (4). To compute multiple voxels, i.e., whole brain process instead of a single voxel, all steps were designed in multidimensional matrices.

After estimating the parameters, the arterial input function (AIF) was determined. Because AIF is usually derived from the MCA region, we needed to identify the MCA from among the major bolus input signals. To locate the MCA region, we generated an index of fast and strong time-intensity signals.

Specifically, the index of each voxel around the circle of Willis was computed using the following equation:

$$index = \frac{1}{2} \left\{ \frac{V_{contrast}}{\max(V_{contrast})} + \left(1 - \frac{V_{BAT} - \min(V_{BAT})}{\max(V_{BAT}) - \min(V_{BAT})} \right) \right\} \quad (5)$$

$V_{contrast}$ represents the differences between the minimum and maximum of the rCTC for each voxel, and V_{BAT} indicates the BAT for each voxel. The circle of Willis was assigned to the region below and in front of the lateral ventricles. We thresholded the index by 0.75, and then, we clustered all thresholded voxels via connected component analysis. The largest component was selected as the MCA region. The AIF was determined as the strongest amplitude of rCTCs in the MCA region. Deconvolution of rCTCs by the AIF was applied using a Fourier transform [28]. Finally, the perfusion

Fig. 3 Intensity adjustment of ADC. **a** Quantiles of ADC values with a red line that indicates the level of adapted thresholding. **b** Raw and adjusted ADC maps

parameters including TTP, CBV, CBF, MTT, and $T_{\max}$ were derived using practical implementation for the measurement of perfusion [29, 30].

Infarct Core Segmentation on DWI

DWI was used to segment the infarct core region. The infarct core segmentation consists of two steps: initial segmentation and false positive reduction (see Fig. 1b). In the first step, for a given ADC map of each subject, we first constructed a quantile curve of ADC intensities within the brain mask. From the quantile-intensity curve, we found an intersection point between two tangent lines with maximum and minimum differential coefficients (Fig. 3a). This intersection point estimates the maximum peak of ADC intensity histogram, that is, the intensity at the point corresponds to the representing intensity of the most dominant tissue (i.e., normal white matter) within the brain mask. The ADC maps were adjusted by dividing the intensities on the ADC map by the intensity at the intersection point (Fig. 3b). This adjustment process makes the intensities of normal white matter tissues converge to one, which could be useful and reliable, especially in accounting for unstable inter-apparatus intensity variability. Then, the adjusted ADC map was thresholded at the optimal absolute threshold value of 0.855. This optimal level of absolute thresholding was empirically determined to maximize the spatial overlap with manual segmentation.

In the second step, we used a b1000 image to remove false positives from the initial segmentation of the first step. For each subject, we computed the global mean and standard deviation (SD) (i.e., μ_{global} and SD_{global}) for b1000 intensities of every voxel within the initial infarct regions. We performed a 3D connected component analysis and computed the mean b1000 value for each infarct component. Then, we determined the component having the mean b1000 value lower than the threshold value T ($T = \mu_{global} - 1.5 \times SD_{global}$) as a false positive component. The final infarct regions were refined by removing the false positive components from the initial infarct regions.

Experiments and Evaluation on PWI and DWI

We determined $T_{\max} > 6$ s as the mutual optimal threshold to identify ischemic penumbra. Although the optimal cutoff value of $T_{\max}$ is still under debate, $T_{\max} > 6$ s delay is most widely used to define the penumbra. The manually segmented masks of the infarct core regions that were drawn by two experts and corrected by a neurologist with more than 10 years experiences were regarded as the gold standard. We measured the spatial overlap index (i.e., Dice coefficient) to evaluate the performance of the segmentation of the penumbra and the infarct core regions. Pearson's linear correlation coefficient was used to compare volumes of the automatically segmented

Fig. 4 Perfusion parameter maps including BAT, TTP, CBV, CVF, MTT, MTT (first moment), theoretical $T_{\max}$, practical $T_{\max}$, 1-index map, and the time between two inflexions of a gamma-variate function

regions using the proposed algorithm and a commercial software with those of manually segmented regions. A threshold for statistical significance was set to $p < 0.05$. We also

Fig. 5 A comparison of the perfusion parameter maps generated using in-house and commercial software

evaluated the biases incurred with the application of an automated segmentation method during volumetric analysis using a Bland-Altman plot.

All algorithms were implemented with Matlab 2015a (The MathWorks Inc. Natick, MA, USA) and run on a Windows 10 Pro with 3.4 GHz Intel Core i7 and 16 GB DDR3 memory.

Results

Perfusion Parameters Estimation on PWI

One subject was omitted from PWI analysis because of a missing phase. First, we visually validated the MCA region detection of 14 cases. Our algorithm successfully detected the MCA for 13 cases, while a false detection case was a posterior cerebral artery.

An example of various perfusion parameter maps, including the BAT, TTP, CBV, CBF, MTT, MTT (first moment), theoretical $T_{\max}$, and practical $T_{\max}$ is provided (Fig. 4). As shown, we provided additional information, such as an index map and the time between two inflection points of a gamma-variate function. The comparison of the perfusion parameter maps with results obtained using a commercially available software, Olea Sphere (Olea Medical, Cambridge, MA, USA), are also shown (Fig. 5).

When we determined $T_{\max} > 6$ s as the mutual optimal threshold to identify ischemic penumbra, the volume of penumbra and perfusion parameter values in the penumbra region are shown (Table 2). Pearson's linear correlation coefficient between penumbra volumes from our method and the commercial software was 0.601 ($p = 0.030$). We also evaluated the performance of the segmentation of the penumbra by thresholding several perfusion parameter maps including practical $T_{\max}$, MTT, MTT (first moment), CBV, and CBF (Table 3). Although we used $T_{\max} > 6$ s as the mutual optimal threshold to identify ischemic penumbra, Dice coefficients with the Olea Sphere were 0.51 ± 0.15 . On the other hand, using $\text{CBF} < 30$ as the threshold, Dice coefficients reached to 0.77 ± 0.08 .

Infarct Core Segmentation on DWI

In the first step of the infarct core segmentation, the adjusted ADC map was thresholded at an absolute threshold value. To determine the optimal threshold value, we tried various values from 0.835 to 0.880 with a step size of 0.005. The final segmentation results reached the best performance with the threshold value of 0.855 (Fig. 6). The Dice coefficient between the manually drawn and automated segmented infarct cores was 0.62 ± 0.18 . Some examples of the results of infarct core segmentation are provided (Fig. 7).

Table 2 Comparison of penumbra volumes and perfusion parameter values in penumbra regions

Parameters	In-house	Commercial
Volume (cc)	64.58 ± 51.93	76.94 ± 45.49
MTT (second)	5.61 ± 1.34	8.61 ± 2.18
MTT: first moment (second)	8.98 ± 1.00	
CBV (ml/100 g)	2.59 ± 1.08	2.77 ± 1.15
CBF (ml/100 g/min)	37.81 ± 12.33	18.76 ± 6.66

The mean infarct volume of the 15 patients was 21.26 ± 22.14 cc according to the gold standard, while the mean of the automatically segmented infarct volumes was 15.56 ± 16.14 cc. The automated segmentation has a proportional bias associated with the volume estimates (Fig. 8). The proposed algorithm can estimate infarct volume with a small proportional bias for a smaller infarct, while the volumes of larger infarcts are more underestimated.

Processing Time

The total processing times per scan were 222.9 ± 16.4 s and 53.4 ± 4.8 s for PWI and DWI, respectively. On the other hand, Olea Sphere roughly took 3 mins for each scan of PWI.

Discussion

For determining treatment strategies in patients with hyperacute stroke, where the benefits are time-sensitive, it is critical to rapidly and automatically detect and quantify the penumbra and the infarct core. In this study, we developed a fully automated and real-time algorithm to segment the penumbra and the infarct core regions based on PWI and DWI.

Although some algorithms that we applied have been introduced in a previous study [22], the infarct core segmentation with adaptive thresholding, automated AIF detection, and details of the perfusion analysis are different. Further, we provide additional information, including an index map and the time between two inflection points of a gamma-variate function. The index map represents voxels that indicate the

Table 3 Dice coefficient for various conditions of perfusion parameter maps

Parameters	Threshold value	Dice coefficient
$T_{\max}$ (second)	> 6	0.51 ± 0.15
MTT (second)	> 6	0.29 ± 0.22
MTT: first moment (second)	> 6	0.68 ± 0.16
CBV (ml/100 g)	< 3	0.54 ± 0.17
CBF (ml/100 g/min)	< 30	0.77 ± 0.08

Fig. 6 A threshold parameter experiment to determine an optimal threshold value for adjusted ADC maps

shortness of the BAT and the amplitude of the time-intensity signal. In the map of the time between inflections, a shorter time interval indicates a sharper gamma-variate function. For example, the ischemic penumbra regions were visualized as the lower index (the higher 1—index) and the longer time interval of inflections in Fig. 4.

There are three main differences between this and previous studies. The first is the gamma-variate cerebrovascular

parameterization of time-variate signals. Although the best parameterization is iterative fitting, it is very time-consuming. To streamline this process, we used a restricted parameters curve-fitting scheme, which could be solved rapidly with parallelism. Second, this algorithm can be used to determine the MCA region. This differs from the approach of a previous study [31] as it offers a theoretical determination, rather than an empirical approach. Therefore, it can be applied to multicenter datasets. The last difference is our simple but robust infarct core segmentation algorithm. Because the brain of each patient contains a certain portion of infarction with lower ADC values, the adjustment of the ADC map using the representative intensity of normal tissues is useful and reliable, especially in accounting for unstable inter-apparatus intensity variability. Although we experimentally obtained the optimal absolute threshold value of 0.855 in this study, we believe that the adjustment of the ADC map is helpful to the generalizability of this threshold to data from other scans/centers. However, if an infarct area is extremely large (e.g., greater than half of the brain), this approach may still not be optimal.

In the algorithm presented in this study, there are two types of MTTs: an arithmetic MTT and an estimated MTT as the first moment of the gamma-variate function. The arithmetic MTT was calculated by dividing CBF by the CBV and the

Fig. 7 Examples of the results of infarct core segmentation on DWI. **a** ADC map. **b** $b1000$ image. **c** Initial segmentation result. **d** Final segmentation result. **e** Gold standard

Fig. 8 Comparison between manual and segmented volumes of infarct core regions

MTT (first moment) was determined as the time of centroid of the area under the curve of the gamma-variate function. The

MTT (first moment) was delayed by 3–4 s compared with the arithmetic MTT. Because the arithmetic MTT is a ratio between the CBV and CBF, it does not reflect the shape of a time-intensity signal. Alternatively, the MTT (first moment) considers time delay and signal dispersion.

The $T_{\max}$ value was defined as the time-to-peak of the residue function value [32]. However, because the residue function is a descending monotonic function [30], the time-to-peak of the residue function must be “time zero” in any case. There are several approaches to estimate $T_{\max}$ values [21]. In this study, we computed two types of $T_{\max}$, a theoretical $T_{\max}$ value, and a practical one. According to a previous study [29], the theoretical $T_{\max}$ presents the arrival delay that corresponds to BAT, but the practical $T_{\max}$ is affected by the degree of dispersion of the time-intensity signal that corresponds to AIF. The detailed implementation of a theoretical $T_{\max}$ value, and a practical one can be found in [30].

In this study, we compared the perfusion parameters estimation on PWI with those from a commercial software while

Fig. 9 An example of the false identification of penumbra on PWI by a commercial software

we evaluated the infarct core segmentation on DWI by comparing with the manually segmented gold standard. Although we used $T_{\max} > 6$ s as the mutual optimal threshold to identify ischemic penumbra, Dice coefficient with the Olea Sphere was still low as 0.51 ± 0.15 . On the other, using CBF < 30 as the threshold, Dice coefficients reached to 0.77 ± 0.08 . Besides, among the comparison of penumbra volumes and perfusion parameter values in penumbra regions (Table 2), there is a large difference in CBF measurements between our method and the Olea Sphere. According to the additional visual assessment of the results from the Olea Sphere, our neurologist reported that there were cases that the commercial software cannot identify the penumbra regions correctly (Fig. 9). Limitations of the study should be noted. First, the study population of acute stroke patients was relatively small and enrolled from a single center. Besides, only patients with a single infarction of an acute ischemic stroke and without movement artifacts were included. Therefore, we need more data and further validation of this algorithm by expanding this study to a multicenter trial and different populations depending on age, sex, diet, geographical location, and other factors. Additionally, further studies to elicit aspects of cerebral blood temporal dynamics based on parameterized gamma-variate functions may be useful.

In summary, we demonstrate a fully automated and real-time algorithm to segment the penumbra and the infarct core regions based on PWI and DWI, respectively. This program can provide clinical information to aid decision-making, such as whether to apply thrombolysis or not, with fast and robust processing. It may be feasible and useful for clinical application in the emergency room and for clinical practice, requiring only images and reducing the need for the interaction of expert doctors.

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Compliance with Ethical Standards

The study was approved by the local institutional review board. Due to the retrospective nature of the study, written informed consent was waived.

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