R2* Map by IDEAL IQ for Acute Cerebral Infarction: Compared with Susceptibility Vessel Sign on T2*-Weighted Imaging

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ABSTRACT
Background To evaluate the detectability of arterial acute thrombus on R2* map by iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL) IQ compared with T2*-weighted imaging (T2*WI).
Methods Twenty-six patients with acute cerebral infarction who underwent R2* map and T2*WI were reviewed. We performed visual assessment of each sequence regarding the visibility of susceptibility effect reflecting acute thrombus and quantitative evaluation of the thrombus on R2* map.
Results Both R2* map and T2*WI showed susceptibility effect reflecting acute thrombi at the occluded site of magnetic resonance angiography (MRA) in 9 patients. R2* map revealed positive while T2*WI showed equivocal findings in 3 patients due to the surrounding vessel signal intensity. Acute thrombus at distal internal carotid artery (ICA) on R2* map was more clearly detected than that on T2*WI without any apparent susceptibility artifact from the skull base in 4 patients. Most of cardiogenic embolic infarction (CEI) and artery-to-artery embolic infarction (A-to-A) demonstrated positive and most of atherothrombotic infarction (ATI) revealed negative findings on R2* map, although quantitative R2* values of thrombi did not show significant differences between CEI (136.6 /msec) and A-to-A (189.9 /msec) ($P = 0.332$).
Conclusion The detectability of acute thrombus on R2* map is comparable to that on T2*WI. Regarding thrombus at distal ICA, its detectability on R2* map is superior to that on T2*WI. R2* map provide additional information to distinguish between embolic and atherothrombotic infarctions.

Key words central nervous system; embolism/thrombosis; ischemia/infarction; magnetic resonance imaging

Magnetic resonance (MR) imaging plays an important role for acute cerebral infarction to investigate the presence of ischemic lesion, ischemic penumbra and hemorrhagic complication. In addition, it is important to recognize the causes of infarction including cardiogenic embolism, atherosclerotic infarction, and lacunar infarction as early as possible because therapeutic strategies are different depending on each pathophysiology.

T2*-weighted imaging (T2*WI) is a useful MR sequences that enable to detect susceptibility effects such as hemorrhage, calcifications, venous structures including tissue ischemic sign and acute emboli with high sensitivity. Recently, evaluating susceptibility effect of intra-arterial acute thrombus as susceptibility vessel sign is considered to be critical because location, size, or signal intensity of susceptibility vessel sign on T2*WI are the important factors to predict the effectiveness of thrombolytic therapy by intravenous recombinant tissue plasminogen activator (rtPA) and mechanical thrombectomy with endovascular procedure.

Although T2*WI has an advantage of detecting acute thrombi as previously reported, it also has a well-established drawback of this sequence. The image of T2*WI near the skull base can be distorted because of the strong susceptibility artifact, which may decrease the detectability of susceptibility sign near the skull base, such as distal internal carotid artery (ICA), basilar-top and proximal posterior cerebral artery (PCA) segments.

On the other hand, a newly developed multi-echo reconstruction technique, called R2* map, is an algorithm based on 6-point Dixon method, which can correct T2* decay and eddy currents induced phase errors. R2* map can generate quantitative susceptibility-sensitive image and we hypothesize that R2* map will have a potential to detect acute thrombus with high accuracy.

The purpose of the present study is to evaluate the detectability of arterial fresh thrombus on R2* map.
compared with conventional T2*WI in the patients with acute cerebral infarction. To our knowledge, there were only a few investigations to refer to the usefulness of $R^2*$ map in the central nervous system disorders,\textsuperscript{19, 20} and this is the first report to examine the utility of $R^2*$ map in acute cerebral infarction.

**MATERIALS AND METHODS**

**Patients**

This retrospective study analyzed data obtained from all patients with a stroke admitted to our institution between April 2, 2013 and September 30, 2014. Patients were eligible if they met the following criteria: MR imaging including diffusion weighted imaging (DWI), T2*WI, $R^2*$ map by iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL) IQ and 3 dimensional time of flight MR angiography (MRA) performed, at least one occluded intracranial vessel on initial MRA, and cause of brain infarction with intracranial vessel occlusion confirmed from clinical information. Our institutional review board approved this study (approval number 2582), and waived the need for written informed consent because of its retrospective design.

**Imaging examinations**

All MR examinations were performed using a 3T MR system (Discovery MR750w 3.0 T, GE Healthcare, Milwaukee, WI). $R^2*$ map is one of the sequences generated by single scanning of IDEAL IQ. Each scanning parameter of IDEAL IQ for $R^2*$ map, T2*WI, DWI and MRA was as follows: IDEAL IQ: repetition time (TR), 8.3 ms; echo time (TE), six different echoes ranging from 1.2 to 7.2 ms; field of view (FOV), 21 cm; matrix, $256 \times 256$; slice thickness, 2.0 mm; acquisition time, 1 min 47 s. T2*WI: TR, 600 ms; TE, 18 ms; FOV, 21 cm; matrix, $512 \times 512$; slice thickness, 5.0 mm; acquisition time, 1 min 5 s. DWI: TR, 7,000 ms; FOV, 21 cm; matrix, $128 \times 128$; slice thickness, 5.0 mm. MRA: TR, 20 ms; TE, 3.4 ms; FOV, 20 cm; matrix, $384 \times 224$; slice thickness, 1.0 mm.

### Table 1. The summary of clinical data and the results of our study in 26 patients

| Patient | Age (years) | Interval between initial MR imaging and symptom onset (hours) | Cause of brain infarction | Imaging findings | Affected vessel on MRA | T2*WI | $R^2*$ map | Mean $R^2*$ value (fms) |
|---------|-------------|-------------------------------------------------------------|---------------------------|------------------|------------------------|-------|------------|---------------------|
| 1       | 81/M        | 7                                                           | CEI                       | Rt. terminal ICA | Positive               | Positive | 147.78     |
| 2       | 89/F        | 2.5                                                         | CEI                       | Lt. terminal ICA | Not evaluable          | Positive | 240.9      |
| 3       | 70/M        | 3                                                           | CEI                       | Lt. ICA          | Not evaluable          | Positive | 269.26     |
| 4       | 80/F        | 6                                                           | CEI                       | Rt. M1           | Positive               | Positive | 169.95     |
| 5       | 82/M        | 6                                                           | CEI                       | Rt. M1           | Negative               | Negative | –          |
| 6       | 82/M        | 1.5                                                         | CEI                       | Lt. M1           | Equivocal              | Positive | 142.36     |
| 7       | 76/F        | 3.5                                                         | CEI                       | Rt. M2           | Positive               | Positive | 107.08     |
| 8       | 86/F        | 6                                                           | CEI                       | Rt. M2           | Positive               | Positive | 66.39      |
| 9       | 93/F        | 8                                                           | CEI                       | Lt. M2           | Positive               | Positive | 65.7       |
| 10      | 76/F        | 2                                                           | CEI                       | Lt. M2           | Positive               | Positive | 62.83      |
| 11      | 58/F        | 4                                                           | CEI                       | Lt. M2           | Positive               | Positive | 146.53     |
| 12      | 58/M        | 4                                                           | CEI                       | Lt. M2           | Positive               | Positive | 155.39     |
| 13      | 56/M        | 7                                                           | CEI                       | Lt. PICA         | Equivocal              | Positive | 64.73      |
| 14      | 61/M        | 24                                                          | A-to-A                    | Rt. ICA          | Not evaluable          | Positive | 122.75     |
| 15      | 66/M        | 22                                                          | A-to-A                    | Lt. ICA          | Not evaluable          | Positive | 317.71     |
| 16      | 83/M        | 18                                                          | A-to-A                    | Lt. M1           | Positive               | Positive | 194.89     |
| 17      | 71/M        | 7                                                           | A-to-A                    | Lt. M2           | Positive               | Positive | 124.12     |
| 18      | 67/M        | 4                                                           | A-to-A                    | Lt. PICA         | Negative               | Negative | –          |
| 19      | 63/M        | 3                                                           | ATI                       | Rt. M1           | Negative               | Negative | –          |
| 20      | 68/M        | 24                                                          | ATI                       | Rt. M1           | Equivocal              | Negative | –          |
| 21      | 75/F        | 1.5                                                         | ATI                       | Rt. M1           | Equivocal              | Negative | –          |
| 22      | 58/M        | 1                                                           | ATI                       | Lt. M1           | Negative               | Negative | None       |
| 23      | 67/M        | 18                                                          | ATI                       | Lt. M1           | Negative               | Negative | None       |
| 24      | 82/M        | 20                                                          | ATI                       | Rt. M2           | Negative               | Negative | None       |
| 25      | 84/F        | 20                                                          | ATI                       | BA               | Negative               | Negative | None       |
| 26      | 77/F        | 2.5                                                         | ATI                       | Lt. PCA          | Equivocal              | Negative | None       |

ATI, atherothrombotic infarction; A-to-A, artery-to-artery embolic infarction; BA, basilar artery; CEI, cardiogenic embolic infarction; F, female; ICA, internal carotid artery; Lt., left; M, male; MR, magnetic resonance; MRA, MR angiography; M1, horizontal segment of MCA; M2, insular segment of MCA; PICA, posterior inferior cerebellar artery; rt., right; T2*WI, T2*-weighted imaging.
Image analysis
We performed visual assessment of R2*-map and T2*-WI at steno-occluded site of MRA. We divided 4 categories according to the consensus of the 2 neuroradiologists (Y.S. and A.K., with 12 and 4 years of experience, respectively, in diagnostic neuroradiology) as follows: i) positive = definitely visible of susceptibility effect reflecting thrombi; ii) negative = definitely invisible of susceptibility effect reflecting thrombi; iii) equivocal = difficult to distinguish between susceptibility effect reflecting thrombi and other paramagnetic substances, and iv) not evaluable = difficult to evaluate susceptibility effect reflecting thrombi due to susceptibility artifacts arising from skull base.

We also performed quantitative assessment of acute thrombi on R2*-map. Regions of interest (ROI) were defined as areas of susceptibility effect reflecting thrombi on R2*-map and mean R2* values of thrombi were measured in each patient. Each difference of R2* value among stroke subtypes was analyzed with Mann-Whitney U test using SPSS software (version 19.0; SPSS, Chicago, IL). A P value < 0.05 was considered statistically significant.

RESULTS
Twenty-six patients (16 men and 10 women; mean age, 73 years; range, 56–93 years) were enrolled in the present study. The causes of brain infarction with intracranial vessel occlusion were as follows: 13 of cardiogenic embolic infarction (CEI), 5 of artery-to-artery embolic infarction (A-to-A), and 8 of atherothrombotic infarction (ATI). A summary of our results is shown in Table 1.

Both R2*-map and T2*-WI showed susceptibility effect reflecting acute thrombi at the occluded site of MRA in 7 patients with CEI and 2 patients with A-to-A (Fig. 1). R2*-map enabled to show positive findings while T2*-WI showed equivocal findings due to the surrounding vessel signal intensity of thrombus in 3 patients with CEI (Fig. 2). Acute thrombus in terminal ICA on R2*-map is more clearly detected than that on T2*-WI (not evaluable) without any apparent susceptibility artifact from the skull base around thrombus in 2 patients with CEI and 2 patients with A-to-A (Fig. 3).

Both R2*-map and T2*-WI indicated negative findings corresponding to the occluded site of MRA in 1 patient with CEI, 1 patient with A-to-A and 5 patients with ATI. R2*-map showed negative findings, whereas T2*-WI demonstrated slight hypointensity which might reflect the other paramagnetic substances such as artery itself or arterial wall calcification in 2 patients with ATI. The other 1 patient had equivocal finding on both R2*-map and T2*-WI.

For quantitative assessment of susceptibility effect of thrombi, we could trace the margin of emboli as ROI for measuring R2* values (1/T2*, /msec) in 12 of 13 patients with CEI and 2 of 4 patients with A-to-A. Mean R2* values of CEI and A-to-A were 136.6 /msec and 189.9 /msec, respectively. There were no significant differences between them (P = 0.332).

DISCUSSION
Our results showed that R2*-map demonstrated acute thrombus as prominent susceptibility effect with high sensitivity in the patients of CEI and A-to-A embolism. In addition, R2*-map could demonstrate susceptibility effect of ICA embolus, which are difficult to detect on conventional T2*-WI due to the strong susceptibility artifact arising from the skull base. Although quantitative R2* values of thrombi showed no significant difference between CEI and A-to-A, R2*-map showed negative findings at occluded sites in ATI so that it was possible to distinguish between embolic and atherothrombotic infarction.

Fig. 1. 80-year-old female with CEI in the right MCA territory (patient 4).

A, DWI shows restrict diffusion in the right basal ganglia; B, MRA reveals occlusion at horizontal segment of right MCA; C, Corresponding to the occlusion site of MRA, both T2*-WI and R2*-map show prominent susceptibility effect reflecting fresh thrombus; D, CEI, cardiogenic embolic infarction; DWI, diffusion weighted imaging; MCA, middle cerebral artery; MRA, magnetic resonance angiography; T2*-WI, T2*-weighted imaging.
Fig. 2. 82-year-old male with CEI in the left MCA territory (patient 6). DWI demonstrates high signal intensity in the left frontal cortex and insula (A) and MRA reveals occlusion at horizontal segment of left MCA (B). Corresponding to the occlusion site of MRA, $R_2^*$ map can show prominent susceptibility effect reflecting fresh thrombus (D, →), while $T_2^*$WI shows equivocal findings of the susceptibility effect reflecting thrombus because of the neighboring low signal intensity from proximal artery itself (C, ◯). CEI, cardiogenic embolic infarction; DWI, diffusion weighted imaging; MCA, middle cerebral artery; MRA, magnetic resonance angiography; $T_2^*$WI, $T_2^*$-weighted imaging.

Fig. 3. 66-year-old male with A-to-A embolism at left terminal ICA (patient 15). DWI shows high signal intensity in the left occipital cortex (A) and MRA demonstrates left ICA occlusion with decreased in-flow effect of left MCA and left PCA (B). In this case, acute thrombus at left terminal ICA on $R_2^*$ map (D) is more clearly detected than that on $T_2^*$WI (C), without any apparent susceptibility artifact from the skull base around thrombus. A-to-A, artery-to-artery embolic infarction; DWI, diffusion weighted imaging; ICA, internal carotid artery; MCA, middle cerebral artery; MRA, magnetic resonance angiography; PCA, posterior cerebral artery; $T_2^*$WI, $T_2^*$-weighted imaging.

thrombotic and embolic infarctions clearly.

It has been already known that early recanalization rate after intravenous rtPA therapy was low in cases with large proximal arterial occlusions like proximal middle cerebral artery (MCA) and ICA. On CT angiography, clot burden score, which is the scoring system of the length and location of the thrombus, was proposed to predict radiological and neurological outcome for thrombolytic therapy or thrombectomy. Although $T_2^*$WI plays an important role for detecting intra-arterial acute thrombus as susceptibility vessel sign by reflecting the presence of deoxyhemoglobin within the clot, susceptibility artifacts from the skull base often disturb the visibility of susceptibility vessel sign at ICA on $T_2^*$WI. Therefore, our results showed the utility of $R_2^*$ map for detecting thrombus at ICA as well as MCA indicate a potential of $R_2^*$ map to be a novel additional marker predicting the efficacy of intravenous rt-PA or mechanical thrombectomy. Furthermore, since therapeutic strategy was different between embolic and atherothrombotic infarctions, we consider that high specificity of acute thrombus on $R_2^*$ map also results in the selection of optimal therapeutic strategy for acute ischemic stroke.

IDEAL IQ is a commercial software equipped with multi-echo chemical shift based water-fat separation and simultaneous $R_2^*$ estimation techniques applying Dixon method. Using this software, quantitative iron image called $R_2^*$ map, as well as in- and out-of-phase images, water and fat images and fat fraction map, can
be obtained by single scanning with short acquisition time.\textsuperscript{16–18} The technical aspects of IDEAL IQ, especially the short multi-echo acquisitions, lead to the fact that R2* map enables to distinguish slight differences of the T2* decay caused by susceptibility effect and visualize them with reliable image contrast, such as between acute thrombus in ICA and susceptibility artifacts arising from the skull base, or peripheral acute thrombus and neighboring intracranial vessels and vessel wall calcifications.

Although IDEAL IQ has been already used for quantitative evaluation of iron deposition and fat fraction of the liver,\textsuperscript{18} this is the first report that indicates a utility of R2* map by using IDEAL IQ for detecting acute thrombus in the patients with cerebral infarction. We also performed quantitative evaluation of thrombus and no significant difference was found between CEI and A-to-A. Cho et al. previously reported that susceptibility vessels signs on T2*WI were more commonly associated with cardioembolic stroke patients than with other stroke subtypes including large artery atherosclerosis.\textsuperscript{8} Liebeskind et al., on the other hand, reported that susceptibility vessel signs on T2*WI reflected histopathology of thrombi: red blood cell-dominant thrombi determined appearance of susceptibility vessel signs, whereas fibrin-predominant occlusive thrombi determined absence of susceptibility vessel signs.\textsuperscript{12} However, histopathology of thrombi extracted by endovascular mechanical thrombectomy was unrelated to final determination of stroke subtypes.\textsuperscript{12} Therefore, there is not yet a unified view whether the susceptibility effects of thrombi on MR imaging enable to determine stroke subtypes or not. R2* map generated by IDEAL IQ is more sophisticated quantitative susceptibility-sensitive image than conventional T2*WI. We consider that further examination of R2* map with larger sample size may lead to clarify its potential of differentiation between CEI and A-to-A.

Our study has several limitations. First, we used MRA as reference standard of vessel occlusions in this study. MRA is less accurate as a reference for vessel occlusion and recanalization than catheter angiography although this modality has proven relatively accurate in evaluating vessel patency.\textsuperscript{26, 27} Second, we did not consider the difference of signal intensity due to the chronological histopathological change of acute thrombus. However, it is likely to be less important factor than we thought, as long as the each interval from onset to MR examination was relatively short like our study. Third, the sample size was modest especially in the patients of A-to-A embolism. As mentioned previously, larger sample size will be needed to clarify the efficacy of quantitative evaluation of thrombi on R2* map.

In conclusion, the detectability of fresh thrombus on R2* map is almost equal to that on T2*WI. Regarding distal ICA embolism, its detectability on R2* map may be superior to that on T2*WI. Moreover, R2* map can provide additional information to differentiate CEI and A-to-A from ATI.

The authors declare no conflict of interest.

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