T1 Mapping for Differentiating of Haemorrhagic Transformation from Extravasation of Iodine Contrast Agents: A Phantom Study

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ABSTRACT

Objective: To evaluate T1 mapping values in different concentrations of iodine and mixed blood and to simulate the application of T1 mapping in differentiating iodine contrast extravasation and haemorrhage transformation after revascularisation in acute ischemic stroke.

Study Design: A phantom-based experimental study.

Place and Duration of the Study: Department of Radiology, the Second Affiliated Hospital of Soochow University, China, from October 2020 to December 2021.

Methodology: Fresh blood, pure iodine, blood-iodine mixtures (75/25, 50/50, and 25/75 ratios), and diluted iodine (at a concentration of 2.1 mmol I/L) were scanned in a phantom on 3-T MR T1 mapping imaging. A total of 10 layers in the middle section of tubes were scanned. The mean value of T1 mapping and 95% confidence interval for the investigated sample compositions were calculated and compared by ANOVA.

Results: The mean values (95% CI) for fresh blood, [2/3] blood + [1/3] iodine, [1/2] blood + [1/2] iodine, [1/3] blood + [2/3] iodine, and pure iodine were 2108.69 ± 1966.68-2250.71 (ms), 1991.72 ± 1763.22-2220.21 (ms), 1811.62 ± 1614.79-2008.45 (ms), 1624.39 ± 1442.41-1806.37 (ms), 1294.68 ± 1172.92-1416.44 (ms), respectively. The differences between the T1 mapping values of all compositions were significant (p < 0.01), except for fresh blood and the sample consisting of 67% blood. The mean value on T1 mapping (95% CI) was 1294.68 ± 1172.92-1416.44 (ms) in the samples only with diluted iodine, which was significantly different from other investigated samples (p < 0.01). The intra-class correlation coefficient between the two times drawing of radiologist A was excellent (ICC=0.913, p<0.01), and between radiologists A and B was 0.99.

Conclusion: Iodine contrast extravasation in a phantom setting might be distinguished from haemorrhagic transformation using T1 mapping.

Key Words: Acute ischemic stroke, Haemorrhage transformation, Contrast extravasation, Magnetic resonance imaging, T1 mapping, 3T MRI.


INTRODUCTION

According to the most recent Global Burden of Disease 2019, stroke is one of the six most important drivers of increased burden (i.e., the reason for the largest absolute increase in disability-adjusted life years between 1990 and 2019) which largely affect older people.¹ The treatment of stroke makes a vital part of the management of stroke, which is becoming increasingly important. Intra-arterial recanalisation has become a main method of stroke treatment.²

Imaging examination is a regular, also essential method to evaluate the result of interventional therapy. However, the newly developed parenchymal hyper-density after interventional therapy often makes the post-intervention evaluation difficult, because it often shows up in post-intervention CT images (31%-61%).³⁻⁶ Meanwhile, the high-density area visible on CT images is a risk factor for bleeding conversion, as well as for postoperative symptomatic iatrogenic bleeding. For that reason, it is crucial to discern high-density lesions as bleeding or mere contrast extravasation, as the incidence of bleeding after intervention is at least 10.9%, with some studies showing as high as 15%, and mortality as high as 83% if symptomatic.⁵

Due to the similar Hounsfield density, it is difficult to distinguish contrast extravasation from bleeding transformation on CT immediately after intervention (<24 hours).³⁻⁶ Although a few studies had reported that spectral detector CT can be used to accurately distinguish between blood and iodine contrast agents in phantom and clinical settings.⁷⁻⁸ There are also some
limitations in the application of spectral detector CT. The software calculation relies on the assumptions made about the three materials under consideration, to a large extent, if a fourth (or more) material, such as calcium, is present at a certain concentration in a voxel, spectral detector CT cannot separate the component materials, resulting in classification errors. The material decomposition algorithm is ineffective at very high iodine contrast concentrations. CT artefacts such as beam-hardening or metallic artefacts (arising from aneurysm clips or coils) can also interfere with the dual-energy analysis.\(^9,10\)

To the best of the authors’ knowledge, there are few studies differentiating haemorrhage from iodinated contrast by MRI. The aim of this study was to investigate the possibility of using T1 imaging to distinguish bleeding from iodine contrast agents in a phantom model.

**METHODOLOGY**

This experimental study was approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University, China. Fifteen mL Corning centrifuge tubes (Corning Incorporated-Life Sciences) were prepared for diluted iodine (iohexol, 300 mg/mL) samples in normal saline, with concentrations 0.00 mgI/mL, 0.70 mgI/mL, 1.40 mgI/mL, 2.10 mgI/mL, 2.80 mgI/mL, 3.50 mgI/mL, 4.20 mgI/mL, 4.90 mgI/mL, 5.60 mgI/mL, 7.00 mgI/mL, and 14.00 mgI/mL, were scanned in non-contrast CT (GE 64-layer LightSpeed VCT scanner). Their attenuation was recorded for the selection of appropriate iodine concentration to prepare the phantom. Five EDTA-K2 anticoagulant tubes were prepared for the phantom. Each cell was filled with nonionic iodinated contrast agents (iohexol, 300 I mg/mL, at a concentration of 2.1 mmol I/L) diluted with arterial blood in a plastic box full of saline. Blood-iodine mixtures were scanned with following proportions: fresh blood; [2/3] blood + [1/3] iodine; [1/2] blood + [1/2] iodine; [1/3] blood + [2/3] iodine; pure iodine (Figure 1).

The phantom was scanned with a 3T MRI (Siemens, Prisma, Germany) using spin-echo acquisitions with T1 mapping (TR/TE=6.05/2.89ms; slices=18; slice gap=0.6 mm; thickness=3.0 mm; FOV=200×200mm; flip angle=3°; scanning time=74 s) sequences.

The pseudo-color map of phantom T1 mapping was generated on the post-processing platform Syngo.via (Siemens, Prisma, Germany, Figure 1). The regions of interest (ROIs) were manually drawn with a circular area of 0.31 cm\(^2\), and placed in the centre of the tube at some distance from the tube wall. Due to the limitation of the height of tube, a total of 10 layers were scanned in the middle section of the tubes. Each ROI was measured three times on the 1/3/5/7/9 layer by two radiologists (A and B, A draw again one month later), and the average attenuation of ROI was taken as the T1 value (Table II).

SPSS 26.0 was used for statistical analysis (IBM, Armonk, New York). Data consistent with the normal distribution was represented by (x±s), The mean value of T1 mapping and the 95% confidence interval were calculated (Table I) for the investigated sample compositions and compared by means of the ANOVA (Table III). The intra-class correlation coefficient was calculated to evaluate the consistency between two radiologists. A p-value <.05 was considered statistically significant.

**RESULTS**

The mean value (95% CI) for fresh blood, [2/3] blood +[1/3] iodine, [1/2] blood +[1/2] iodine, [1/3] blood +[2/3] iodine, and pure iodine were 2108.69 ± 1966.68-2250.71(ms), 1991.72 ± 1763.22-2220.21(ms), 1811.62 ± 1614.79-2008.45 (ms), 1624.39 ± 1442.41-1806.37(ms), 1294.68 ± 1172.92-1416.44 (ms), respectively, as shown in Figure 2 and Table II. The differences in T1 mapping values in all compositions were significant (p <0.01), except for fresh blood and the sample consisting of 67% blood. The mean value on T1 mapping (95% CI) was 1294.68 ± 1172.92-1416.44 (ms) in samples containing only diluted iodine, which was significantly different from other investigated samples (p < .01). The intra-class correlation coefficient between two times drawing of radiologist A was excellent (ICC=0.913, p<0.01), and between radiologist A and B was close to 0.99.

![Figure 1: Diagram of sample mixtures in the study.](image1)

![Figure 2: T1 mapping value (ms) of sample mixtures. There is a significant incremental decrease of values with decreasing blood content except stale blood. The differences among all compositions were significant (p<0.04), except between fresh blood and the sample consisting of 67% blood.](image2)
### DISCUSSION

Past several studies used phosphate buffered saline in the sample preparation to prevent cytolysis, and packed red blood cells of different hematocrit to simulate changes in haemorrhage.\(^{8,11,12}\) Due to the possibility that phosphate-buffered saline could affect the exact chemical status of blood and iodine potentially, the present researchers used saline solution and arterial blood for sample preparation, both of them were closer to the physiological state. In addition, anticoagulant tubes for the phantom used heparin buffered saline could affect the exact chemical status of haemorrhage.

The 2018 American Heart Association /ASA guidelines emphasise the importance of intravenous thrombolytic delivery for every eligible patient who is considering thrombectomy. An important addition for patients with intravascular tandem occlusion (possible posterior circulatory ischemia) is the new IIb recommendation to support the use of antiplatelet therapy within the first 24 hours of tPA therapy if there are concurrent complications (discontinuation of this therapy poses a significant risk).\(^{11}\)

Although the routine use of thrombolytics or antiplatelet agents before thrombectomy is controversial, neurologists feel it to be safe to routinely use antiplatelet agents before thrombectomy. EDTA-K2 does not replace antiplatelet agents.
agents and heparin sodium, but both have the effect of preventing thrombosis. Patients at the study centre proceed for CT scanning immediately after thrombectomy. Based on the above points, the model approximated the early state after endovascular thrombectomy.

After careful and thorough evaluation of the patients undergoing CT scan after endovascular therapy for acute ischemic stroke and its follow-up, 2.1 l mol/L was selected for sample preparation, as its CT attenuation (63–84 HU) was the closest to the iodine extravasation. This does not agree well with the observations of prior investigators. It is inferred that this may be caused by differences in machines and the complexity of the mixture.

A handful of reports had been published addressing the use of single- or dual-source dual-energy CT in differentiating blood from iodinated contrast. Radiologists use visual evaluation of these studies to distinguish between high density on conventional head CT images as bleeding or iodine. Although intracranial haemorrhage is typically dense (>50 HU), it may be associated with lower density due to anticoagulation, cerebrospinal fluid with arachnoid tears, or severe anaemia (e.g., sickle cell anaemia), which may complicate subjective assessment.

T1 mapping has been rapidly popularised as a form of tissue characterisation using parameterised methods. With the development of different sequences, image acquisition has been integrated into clinical routine, especially in cardiovascular magnetic resonance (CMR). Recently, Qi et al. developed a 3D (3D) time-efficient sequence with a high spatial resolution for quantitative vascular wall T1 mapping to characterise SNAP imaging and 3D golden Angle radial K-space sampling (GOAL). This method has a good correlation with the traditional 2D inversion recovery spin echo method in the measurement of phantom T1. Qiao et al. use CMR vessel wall imaging including 3D T1 mapping sequence (GOAL-SNAP) to validate the usefulness of vivo T1 mapping in assessing carotid vulnerable plaque components by histology. In addition, it was reported that it is possible to distinguish contrast staining from bleeding transformation by a post-intervention DWI protocol immediately that includes a gradient recall echo sequence.

To the best of the author’s knowledge, this study used T1 mapping technique to perform quantitative analyses and evaluation in distinguishing haemorrhage from iodine in a phantom model. These results showed that the difference between fresh blood and pure iodine was significant (p<0.01), which demonstrates that T1 mapping had the ability to differentiate blood from iodinated contrast. Although the difference between fresh blood and two-part blood + one-part iodine was not significant, which may suggest that T1 mapping is sensitive to minor haemorrhage. Therefore, patients may benefit from the early detection of haemorrhage, and monitoring its progression.

Good consistency is the precondition for the wide application of T1 mapping in differentiating iodine from the blood. The higher the consistency, the better the confidence and repeatability of T1 mapping. This study’s results show that the consistency between the two radiologists was excellent.

There are several limitations to this study. First, the work used anticoagulated blood mixed with a diluted iodinated contrast agent. This may not be representative of the pathology. It was attempted to mimic the early mixture with antiplatelet drugs and sodium heparin. A larger sample size is needed to verify the study in the later stage. Third, in the future, clinical data is required to make the study more complete. An evenly mixed mixture to get the best ROI picture may not always be the case in a clinical setting.

CONCLUSION

The preliminary results show that iodine contrast extravasation in a phantom setting might be distinguished from bleeding transformation using T1 mapping.

ETHICAL APPROVAL:
The study was conducted after obtaining approval by the Ethics Committee of the Second Affiliated Hospital of Soochow University.

PATIENTS’ CONSENT:
Not applicable.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS’ CONTRIBUTION:
RL: Guarantor of the integrity of the entire study and manuscript editing.
RL, CW: Study concept and design.
WC: Literature search.
RL, CS: Clinical studies.
RL, SH: Equal contribution in the experimental study and data analysis.
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