MR Perfusion Imaging: Half Dose Gadolinium Is Half The Quality

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Abstract

Background and Purpose
Patients with acute ischemic stroke due to a large vessel occlusion (AIS-LVO) undergo emergent neuroimaging triage for thrombectomy treatment. MRI is often utilized for this evaluation, and cerebral magnetic resonance perfusion (MRP) imaging is used to identify the presence of the salvageable penumbra. To determine if dose reduction is feasible, we assessed whether a half-dose reduction in gadobenate provided sufficient MRP quality in AIS-LVO patients.

Methods
A prospective observational study of all patients presenting to our neurovascular referral center with AIS-LVO was performed. MRP was done with a half-dose of gadolinium (0.1 ml/kg body weight) over a period of 10-months. MRP images were compared to a consecutive historical cohort of full dose gadolinium (0.2 ml/kg body weight) MRP studies and rated for image quality (poor, borderline, or good) that determined thrombectomy eligibility.

Results
54 half-dose and 127 full-dose patients were included. No differences in patient demographics or stroke presentation details were identified. MRP quality differed between half- and full-dose scans (p<0.001), which were rated as poor (40.7% versus 6.3%), borderline (18.6% versus 26.8%) and good quality (40.7% versus 66.9%), respectively. MRP image quality was then dichotomized into poor and sufficient (borderline and good) quality groups; half-dose studies were more likely to have poor quality compared to full-dose studies (40.7% versus 6.3%; p<0.001).

Conclusions
Half-dose gadolinium administration for MRP in AIS-LVO patients results in poor image quality in a substantial number of studies. MR cerebral perfusion performed with half-dose gadolinium may adversely affect stroke patient triage for thrombectomy.
Introduction

Endovascular thrombectomy is an effective treatment of acute ischemic stroke (AIS) caused by large vessel occlusion (LVO) of a cerebral vessel.\textsuperscript{1-3} AIS patients most likely to benefit from thrombectomy are those selected by magnetic resonance imaging (MRI)\textsuperscript{4} and cerebral perfusion imaging using computed tomography or magnetic resonance techniques.\textsuperscript{2,3,5-7} These advanced imaging techniques identify patients with a target mismatch (TMM), which refers to a relatively small infarct core volume with a large penumbra that is at risk of infarction if thrombectomy is not successfully performed. As a result of these randomized trials, cerebral perfusion imaging has become a routine study in most radiology practices.

MRP is performed with dynamic susceptibility contrast imaging following intravenous injection of a gadolinium-based contrast agent. There have been multiple reports of gadolinium deposition in the brain tissue following repeated intravenous injection of this contrast agent.\textsuperscript{8-13} While there is a lack of evidence that this deposition is clinically significant, the Food and Drug Agency has recommended limited use of gadolinium contrast agents when possible.\textsuperscript{14} Therefore, imaging protocols that reduce gadolinium dosage are increasingly being implemented.

Prior studies have suggested that MRP performed with a 50% reduction in gadolinium contrast agent dose generates imaging maps that are similar to full-dose studies.\textsuperscript{15-18} and off-label half-dose gadolinium studies are often performed at our institution in non-acute cases during which a concomitant post-contrast MR Angiogram of the neck is obtained. In addition, some centers may reduce the gadolinium dose for magnetic resonance perfusion (MRP) when a post-contrast MR angiogram of the neck is also performed to minimize the total gadolinium dose. However, whether MRP performed with a 50% reduction in gadolinium dose still allows for determination of a TMM in AIS patients with a LVO has not
been well studied. We hypothesized that cerebral MRP performed with half-dose gadolinium would provide image maps that were of non-inferior quality to full dose studies. Therefore, we determined whether MRP performed with half-dose gadobenate adequately identifies AIS patients with a TUM compared to those performed with full-dose gadolinium.

**Methods**

This prospective observational study with a retrospective control cohort was approved by our institutional internal review board and complied with the Health Insurance Portability and Accountability Act. The need for patient consent was waived by our institutional internal review board.

**Patients in Study**

We performed study of patients who underwent endovascular thrombectomy triage for an acute ischemic stroke due to a presumed large vessel occlusion based upon patient symptoms at our stroke center. We prospectively collected data in AIS patients who underwent MRP with intravenous gadolinium contrast (529 mg/ml; MultiHance, Bracco, Milan, Italy) administered at half dose (0.1 ml/kg body weight) over a ten-month period (January 8, 2019 to October 29, 2019). We identified a historical comparison cohort of consecutive AIS patients who underwent MRP with intravenous gadolinium contrast (529 mg/ml; MultiHance, Bracco, Milan, Italy) administered at full dose (0.2 ml/kg body weight) between January 5, 2017 and September 5, 2018. These two groups were compared for the study analysis.

Inclusion criteria were: patients aged ≥18 years, presentation within 24-hours of
symptom onset, symptoms consistent with an anterior circulation AIS-LVO, imaging evaluation with brain MRI that included diffusion-weighted imaging (DWI), gradient-echo (GRE), time-of-flight magnetic resonance angiography (MRA), arterial spin labeling (ASL), and dynamic susceptibility contrast susceptibility magnetic resonance perfusion sequences. Exclusion criteria included patients triaged without MRP and excessive motion artifact during the MRI study. All patients who met these criteria during the enrollment period were included.

ASL was used for penumbral tissue identification in the event that MRP image quality was insufficient at the time of patient treatment, and no treatment decisions were based upon poor MRP image quality during the period of the study. TMM presence in these ASL cases was based upon a visual comparison of the ischemic core relative to the perfusion deficit on ASL. In addition, a mismatch between the ischemic core and the patient symptoms, as measured on the National Institutes of Health Stroke Severity (NIHSS) scale was used to determine the presence of a TMM in patients without interpretable MRP. The use of ASL and core-NIHSS mismatch are standardly used at our institution for all instances in which MRP fails technically for any reason.

**MRI Acquisition Details**

All studies were acquired on a 1.5T GE Signa or 3.0T GE MR750 MRI scanner (GE Healthcare, Milwaukee, Wisconsin).

MRI (3 Tesla) sequence parameters for the were as follows. (1) Axial DWI: single-spin-echo: 5mm; skip 0mm; repetition time (TR) =6000 msec, Echo time (TE)=78.2 msec; b-value=0 and 1000 sec/mm²; flip angle 90°. (2) MRP: 5mm, skip 0mm; TR=1800 msec, TE=35 msec; flip angle 80°. MRI (1.5 Tesla) sequence parameters for the were as follows.
(1) Axial DWI: single-spin-echo: 5mm, skip 1.5mm; TR=7700 msec, TE=85.2 msec; b-value=0 and 1000 sec/mm^2; flip angle 90°. (2) MRP: 5mm, skip 0mm; TR=1800 msec, TE=40 msec; flip angle 60°. MRP was performed following the intravenous administration of Multihance (Bracco, Milan, Italy) into an antecubital vein at a rate of 4.0 ml/sec using a power injector at the doses noted above with a 25 ml saline chase at 4.0 ml/sec. All images were acquired 15 seconds after injection with 5 mm slice thickness, and imaging coverage extended from the vertex to the occiput. (3) ASL: TR/TE (5500/2.5 ms) with a pseudo-continuous labeling period of 1500 ms with a post-label delay of 2000 ms. ASL labeling was at the level of the foramen magnum. ASL images were displayed on a three-dimensional background suppressed fast-spin echo sequence with in-plane resolution of 3 mm and a through-plane resolution of 4 mm. (4) Axial gradient-echo (TR/TE 600/30 ms). (5) Axial time-of-flight MRA (TR/TE 34/3.1 ms, field of view 24 cm, matrix 512 x 128, slice thickness 1 mm).

Clinical and Imaging Analysis

Patient demographic, stroke presentation, and stroke treatment details were determined from a prospectively maintained AIS patient database.

All MRI data were automatically processed by RAPID (iSchemaView, Menlo Park, CA) to determine core infarction and ischemic penumbra volumes. The ischemic core was defined as the volume of tissue with an apparent diffusion coefficient signal intensity <620 x10^-6 mm^2/second, and penumbra was defined as the difference between the volume of tissue with a time-to-maximum of the tissue residue function delay of >6 seconds (Tmax >6s) on MRP and the ischemic core volume. TMM was defined as a core infarction <70 ml with a corresponding penumbra that was larger than at least 15 ml and a Tmax >6s/core volume ratio of at least 1.8.19

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MRI and MRP images were anonymized and had the date of scan set to a uniform value to blind to gadolinium dose. They were reviewed by two diagnostic and interventional neuroradiologists with 7 and >30 years of experience who were blinded to patient details and gadolinium dose. Each reader independently reviewed all MRP images, which included the Tmax maps and the RAPID Summary map, which shows the segmented Tmax>6s and the DWI core volumes. Readers assigned a quality score for each subject that was based upon whether the reader could reliably detect the presence of a TMM to guide a thrombectomy treatment decision as: (1) unable to make a TMM determination due to the inability to determine the laterality of the penumbra on Tmax>6s maps or an inability to determine the contour of the penumbra on Tmax>6s maps (poor quality), (2) able to make a TMM determination with difficulty due to some uncertainty as to the contour of the penumbra on Tmax >6s maps (borderline quality), or (3) easily able to make a TMM determination given clear delineation of the penumbra contours on Tmax>6s that were larger than the ischemic core on DWI (good quality). Reader discrepancies were resolved by consensus.

Dichotomized MRP quality score was considered good for good and borderline quality studies and poor for poor quality studies.

**Statistical Analysis**

Continuous variables were compared by Student t-test and Mann-Whitney U test. Differences in proportions were assessed using $\chi^2$ test with Fisher’s exact statistics applied where needed. To assess a trend of the imaging quality on the 3-point ordinal scale between high/low dose we used Cochran-Armitage test. Inter-rater agreement was determined using a chance-corrected agreement coefficient kappa score. Alpha was set at the 0.05 level, and all reported results are two-sided. Statistical analysis was done using SAS 9.4 and IBM SPSS 26.
Results

A total of 54 half-dose and 127 full-dose MRP studies were included in this study. Most patients underwent MRI on a 3.0 Tesla scanner (n=170; 94%), and 11 patients (6%) underwent imaging on a 1.5 Tesla MRI. No patients were excluded due to excessive patient motion. Patient demographic and stroke presentation details are presented in Table 1, and there were no significant differences between half-dose and full-dose patients.

Overall, MRP studies were rated poor in 30 (16.6%), borderline in 44 (24.3%), and good in 107 (69.1%) of patients. Agreement between two raters was moderate (kappa=0.52 [95% CI, 0.42-0.62]). 33 cases underwent a consensus evaluation, and all of these cases were rated as borderline or poor by at least one of the raters. There was a significant difference in MRP quality between full-dose and half-dose gadolinium groups (p<0.001; Table 2); in half-dose studies, poor quality was more common (40.7% versus 6.3%), whereas borderline (18.5% versus 26.8%) and good quality (40.7% versus 66.9%) were less common compared to full-dose patients.

MRP study quality was then dichotomized as good score (good and borderline quality) and poor score (poor quality) groups, and these dichotomized scores were compared between half-dose and full-dose gadolinium patients. Half-dose studies were more likely to have poor quality MRP compared to full-dose studies (40.7% versus 6.3%; p<0.001) (Figure 1).
Discussion

In this study, we found that brain MRP studies performed with gadolinium administration at half-dose (0.1 mg/kg bodyweight) are inferior in quality to studies performed with full-dose gadolinium (0.2 mg/kg bodyweight). The neuroradiology readers in our study were unable to confidently determine a TMM profile and thrombectomy eligibility in 40.7% of patients who underwent a half-dose MRP study compared to 6.3% of patients who underwent a full-dose MRP study. Our findings suggest that caution should be exercised in reducing gadolinium dose for MRP studies in AIS-LVO patients undergoing thrombectomy triage.

The neuroimaging evaluation of AIS-LVO patients is critical to determine whether a patient is a candidate for treatment by endovascular thrombectomy. Cerebral perfusion imaging by CT or MRI is playing an increasingly role in the evaluation of these patients following the publication of several randomized trials that have shown favorable outcomes in patients treated by thrombectomy in early\textsuperscript{6,7,20-22} and late time\textsuperscript{2,3} windows. Neuroimaging protocols still vary widely by location, but patients who undergo evaluation by MRI have better outcomes than patients evaluated by CT in early time windows (0-6 hours after symptom onset).\textsuperscript{4} The benefit of penumbral imaging in patients undergoing thrombectomy treatment in early time windows remains controversial,\textsuperscript{4} but studies that used cerebral perfusion imaging in this time window had higher rates of a good functional outcome\textsuperscript{6,7} compared to studies that did not use perfusion imaging.\textsuperscript{20-22} Cerebral perfusion imaging by CT or MRI is recommended in patients undergoing thrombectomy triage in late time windows (6-24 hours).\textsuperscript{2,3,5,23}

Several reports have described gadolinium deposition in the dentate nucleus and globus pallidus following serial MRI studies and have raised concern for the safety of intravenous gadolinium administration.\textsuperscript{8,10-13} The significance of these early observations remains unknown, but many centers have explored the use of gadolinium dose reductions in
their imaging protocols in an attempt to mitigate any potential risks of gadolinium exposure. The results of our study suggest that gadolinium dose reductions in cerebral MRP protocols may result in a significant increase in the frequency of suboptimal or uninterpretable perfusion images, which may potentially negatively impact the treatment of these critically ill patients. Our imaging protocol includes ASL as a secondary means to estimate penumbral tissue, but MRP and ASL are not always performed together. The lack of a secondary means to identify patients with a core infarction that is matched in size to the penumbra may lead to unnecessary thrombectomy treatment and potential harm to the patient. Therefore, all failures of TMM identification due to half-dose gadolinium may negatively impact thrombectomy patient triage.

Our results differ from prior studies that found no significant difference in cerebral MRP image quality after full-dose versus reduced-dose gadolinium administration. However, only one of these studies, that included only 10 patients, evaluated the Tmax parameter that is increasingly used for penumbra delineation. Whether the differences in cerebral perfusion image parameter images, image processing software, or study methods might explain these differing results requires additional study.

The manner in which the half-dose studies with poor image quality would have impacted patient treatment decisions outside of our study design is speculative. The inability to identify the presence of a TMM profile may lead to inadvertent treatment or exclusion depending upon the imaging results. Our study was designed so as not to influence patient treatment decisions by the inclusion of ASL for penumbra delineation, and patients with a discernable TMM profile on MRP or ASL who were appropriate candidates underwent treatment per our standard clinical practice.

Our study has several limitations. The retrospective design and relatively small sample size may introduce bias. The lack of a concurrent control population may also introduce bias into the results. The study was performed at a single neurovascular referral
center and images were analyzed using a single cerebral perfusion software vendor platform, both of which may limit the generalizability of our results. The study was conducted with a single gadolinium agent, and whether these results apply to other gadolinium agents with different relaxivity requires further study. Although we did not detect any influence of field strength or head coil in our analysis, these variables may confound our results for a minority of patients.

In conclusion, half-dose gadolinium administration for MRP in AIS-LVO patients results in poor image quality in a high number of patients (40.7%) that may limit accurate patient triage to thrombectomy treatment. Caution should be exercised in reducing gadolinium dose for MRP in these patients that require emergent treatment.
References


24. Calamante F, Christensen S, Desmond PM, Ostergaard L, Davis SM, Connelly A. The physiological significance of the time-to-maximum (Tmax) parameter in perfusion MRI. Stroke 2010;41:1169-74.
Table 1: Patient clinical and stroke presentation details.

<table>
<thead>
<tr>
<th></th>
<th>Half-Dose n=54</th>
<th>Full-Dose n=127</th>
<th>p-value</th>
<th>n Missing/Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>19 (35.2)</td>
<td>60 (47.2)</td>
<td>0.134</td>
<td>0</td>
</tr>
<tr>
<td>Coronary Artery Disease, n (%)</td>
<td>9 (16.7)</td>
<td>17 (13.4)</td>
<td>0.852</td>
<td>0</td>
</tr>
<tr>
<td>Atrial Fibrillation, n (%)</td>
<td>22 (44.0)</td>
<td>43 (34.7)</td>
<td>0.251</td>
<td>7</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>14 (26.4)</td>
<td>40 (32.3)</td>
<td>0.439</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>40 (74.1)</td>
<td>89 (70.6)</td>
<td>0.720</td>
<td>1</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>26 (48.1)</td>
<td>60 (48.0)</td>
<td>1.0</td>
<td>2</td>
</tr>
<tr>
<td>Prior ischemic stroke, n (%)</td>
<td>8 (14.8)</td>
<td>20 (16.0)</td>
<td>0.842</td>
<td>2</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td></td>
<td></td>
<td>0.317</td>
<td>12</td>
</tr>
<tr>
<td>Never</td>
<td>32 (61.5)</td>
<td>68 (58.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>4 (7.7)</td>
<td>19 (16.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior</td>
<td>16 (30.8)</td>
<td>30 (25.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous tissue Plasmionogen Activator, n (%)</td>
<td>30 (55.6)</td>
<td>73 (57.5)</td>
<td>0.811</td>
<td>0</td>
</tr>
<tr>
<td>Age in years, mean±SD</td>
<td>67.5±14.2</td>
<td>66.4±17.1</td>
<td>0.676</td>
<td>0</td>
</tr>
<tr>
<td>Presentation NIHSS, median (IQR)</td>
<td>16 (10-19)</td>
<td>17 (11-22)</td>
<td>0.107</td>
<td>0</td>
</tr>
<tr>
<td>Core Infarct volume, mL, median (IQR)</td>
<td>14 (0-42)</td>
<td>23 (0-49)</td>
<td>0.103</td>
<td>1</td>
</tr>
<tr>
<td>Tmax&gt;6s volume, mL, median (IQR)</td>
<td>71 (14-112)</td>
<td>74 (28-123.5)</td>
<td>0.596</td>
<td>0</td>
</tr>
</tbody>
</table>

ml, milliliter; n, number; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; IQR, inter quartile range.
### Table 2: Neuroradiologist scoring of MRP quality stratified by gadolinium dose.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Consensus Score</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Poor</td>
<td>Borderline</td>
</tr>
<tr>
<td>Full</td>
<td>8</td>
<td>34</td>
</tr>
<tr>
<td>% within Dose</td>
<td>6.3%</td>
<td>26.8%</td>
</tr>
<tr>
<td>Half</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>% within Dose</td>
<td>40.7%</td>
<td>18.5%</td>
</tr>
</tbody>
</table>

There was a significant difference in the image quality between studies performed with full versus half dose gadolinium (p<0.001).
Figure Legends

Figure 1. Representative examples of image quality in full-dose and half-dose gadolinium cerebral perfusion studies.

(A-B) Full-dose gadolinium cerebral perfusion results in good image quality in patients with a left M1 occlusion. (C-D) Half-dose gadolinium cerebral perfusion results in poor image quality, which is characterized by noise, perfusion delays in both hemispheres, and multiple areas of image drop out (white pixels). Pink denotes the ischemic core. Green denotes the penumbra. ADC, apparent diffusion co-efficient; M1, first segment of the middle cerebral artery.
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