Prediction of hemorrhagic transformation in acute ischemic stroke: a comparison of DSC surrogate measures of permeability

R. E. Thornhill1,2, S. Chen1, W. Rammo1, D. J. Mikulis1,3, and A. Kassner1,2
1Medical Imaging, University of Toronto, Toronto, Ontario, Canada, 2Physiology and Experimental Medicine, Hospital for Sick Children, Toronto, Ontario, Canada, 3Medical Imaging, Toronto Western Hospital, Toronto, Ontario, Canada

INTRODUCTION:
The clinical use of tissue plasminogen activators (e.g.(rt-PA)) in acute ischemic stroke (AIS) is limited to patients who present < 4.5h of symptom onset [1]. Beyond this benchmark, rt-PA is known to increase the risk of blood-brain-barrier (BBB) disruption and bleeding into the surrounding tissue or ‘hemorrhagic transformation’ (HT). What is needed for successful treatment guidance is a method for identifying patients at increased risk of HT. Advances in permeability estimation with dynamic contrast-enhanced (DCE) MRI can delineate areas of BBB disruption and thereby identify patients at increased risk of HT [2]. An alternative to DCE and permeability estimation is a model-free approach to measure the relative recirculation of contrast (rR), which we can extract from dynamic susceptibility contrast (DSC) data-sets [3]. It has been previously shown that this measure can achieve sensitivity and specificity similar to DCE-MRI for the prediction of HT [4]. However, a number of other DSC-based surrogate measures of BBB permeability have been proposed in the literature, including Peak Height, % Recovery [5], and the Slope of the ΔR2 v. time curve between 50 and 60 seconds post-injection [6]. The purpose of this study was to evaluate the performance of these DSC-based parameters in discriminating between patients who will proceed to HT and those who will not.

MATERIALS AND METHODS:
Eighteen patients (aged 27-89 years) with a working diagnosis of AIS were examined <6h of symptom onset. MRI was performed on a 1.5T MR system (GE Healthcare, Milwaukee, USA) equipped with Echo-Speed gradients and an 8-channel head coil. A DSC protocol with a T2*-weighted single-shot EPI acquisition was performed with the following parameters: TR 1725ms, TE 31.5ms, FOV 240mm, Matrix 96 X 64, Flip Angle 90º, slice thickness 5mm. The total acquisition time for 50 dynamics was 86 s. Gadodiamide was injected as a bolus (0.1mmol/kg Omnisec, GE healthcare, USA) immediately following initiation of the T2*W sequence. HT was determined by follow-up CT and/or MRI 24-72 h after initial imaging. Data were analyzed on an independent workstation, using in-house software (MR analyser v. 4.0) developed in MATLAB. Two regions of interests (ROI) were defined on the DWI images, one placed within the core region of the DWI abnormality (infarct) and the second within the homologous location in the contralateral hemisphere. DWI ROIs were then compared to the equivalent DSC image-set. In addition to rR [3], the DSC parameters investigated included Peak Height and % Recovery [5], as well as the Slope of the ΔR2 v. time curve between 50 and 60 seconds post-injection [6] (FIG. 1). Mean values for each parameter were recorded and patients were grouped based on HT-status at follow-up. For each DSC parameter, differences between infarct and contralateral ROIs were assessed for significance using Wilcoxon matched pairs tests. Mann-Whitney U tests were used to assess differences between HT and no-HT patients for each parameter. Finally, the relationship between rR and each of Peak Height, % Recovery, and Slope was investigated using linear regression.

RESULTS:
Eight out of 18 patients proceeded to HT. Mean values for each of the four parameters investigated are listed in TABLE 1. While the mean rR for infarct ROIs was significantly greater than for contralateral ROIs, the converse was true for % Recovery (P<0.001 for each comparison). Similarly, the mean rR for HT infarct ROIs was significantly greater than for non-HT ROIs, while the mean % Recovery in HT patients was significantly lower than for those without hemorrhagic complications. Logistic regression revealed a negative correlation between % Recovery and rR (r=0.875, P<0.001). No significant differences were detected with respect to % Recovery between HT and non-HT patients. Neither Peak Height nor Slope was found to be significantly correlated with rR.

DISCUSSION:
Of the four DSC-based parameters investigated in this study, only rR and % Recovery were capable of discriminating between HT and non-HT infarcts. Unlike Bang and colleagues, we were unable to distinguish between HT and non-HT patients using the 50-60 s Slope parameter [6]. While the rR results are supported by a previously published study [4], this is the first time (to our knowledge) that the % Recovery of the ΔR2 v. time curve between 50 and 60 seconds post-injection [6] (FIG. 1). Mean values for each parameter were recorded and patients were grouped based on HT-status at follow-up. For each DSC parameter, differences between infarct and contralateral ROIs were assessed for significance using Wilcoxon matched pairs tests. Mann-Whitney U tests were used to assess differences between HT and no-HT patients for each parameter. Finally, the relationship between rR and each of Peak Height, % Recovery, and Slope was investigated using linear regression.

TABLE 1:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Contra.</th>
<th>Infarct</th>
<th>HT</th>
<th>no HT</th>
<th>Pearson’s r (v. rR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rR</td>
<td>0.08 ± 0.01</td>
<td>0.18 ± 0.02</td>
<td>0.22 ± 0.06</td>
<td>0.14 ± 0.06</td>
<td>---</td>
</tr>
<tr>
<td>Peak Height</td>
<td>9.17 ± 3.50</td>
<td>8.15 ± 3.37</td>
<td>7.95 ± 2.20</td>
<td>7.41 ± 3.24</td>
<td>-0.362</td>
</tr>
<tr>
<td>% Recovery</td>
<td>91 ± 3</td>
<td>79 ± 9</td>
<td>76 ± 6</td>
<td>82 ± 11</td>
<td>-0.875</td>
</tr>
<tr>
<td>Slope</td>
<td>-0.02 ± 0.05</td>
<td>-0.02 ± 0.06</td>
<td>-0.02 ± 0.07</td>
<td>-0.02 ± 0.06</td>
<td>-0.180</td>
</tr>
</tbody>
</table>

All values represent mean ± SD; *P < 0.001 v. Contra.; †P < 0.001 v. HT; ‡P < 0.05 v. HT; § P < 0.001 for Pearson’s r.

REFERENCES:

FIG. 1: A ΔR2 v. time curve (ΔR2(measured)), as well as its gamma-variate fit (ΔR2(fit)). Four DSC parameters were calculated: rR (C/A), Peak Height (A), % Recovery = 100 x (A-B)/A, and Slope = slope of ΔR2(measured) (t) between 50 and 60 s post-injection.