GRE vs. PWI for Hemorrhage and Intravascular Clot Detection: A Retrospective Analysis of the DEFUSE2, EPITHET and SENSE 3 Datasets

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TARGET AUDIENCE: Clinicians and physicists interested in cerebrovascular disease.

PURPOSE: Acute hemorrhage is a contra-indication to acute stroke therapy with iv-thrombolytics, therefore its detection is crucial. However, in *acute ischemic stroke* (AIS), detection of hemorrhage must be balanced against the need for fast imaging, due to the time-critical nature of salvaging brain tissue. Conventional T_2*-weighted *gradient-echo* (GRE) MRI allows detection of paramagnetic blood products, and is the mainstay of hemorrhage detection on MR but unfortunately it can add up to 5 minutes to the AIS protocol, and remains one of the slowest and most motion-sensitive sequences in the protocol. *Dynamic susceptibility contrast* (DSC) GRE EPI, which is used for *perfusion-weighted imaging* (PWI), is also a key component of contemporary AIS protocols. DSC GRE PWI is inherently T_2*-weighted, and is therefore expected to be sensitive for hemorrhage detection. **The aim of this study is therefore to compare conventional GRE and GRE DSC PWI (first few time points), to establish whether PWI is at least of equivalent accuracy to GRE for the detection of hemorrhage and intravascular clot.** If equivalence can be established, GRE can be omitted from the AIS protocol entirely, saving time and therefore improving the chances of a good outcome. The secondary aim is **to determine the accuracy of DSC GRE PWI and GRE for the detection of intra-arterial thrombus, against the gold-standard of *digital subtraction angiography* (DSA), and to determine whether DSC GRE PWI and GRE are equivalent for this task.** Many radiologists examine the intra-cranial arteries for the presence of thrombus on GRE; this adjunctive information can help differentiate between chronic steno-occlusive disease and an acute thrombo-embolic vascular occlusion, which can be difficult to see on TOF MRA. This is clinically relevant, as acute thrombo-embolic disease may require intra-arterial catheter-based treatment.

METHODS: • *Patient population:* The datasets from 3 large stroke studies: DEFUSE 2 [1], EPITHET [2] and SENSE 3 (ongoing) were retrospectively analyzed. All MRI studies with both GRE DSC PWI and conventional GRE from these trials were included: 375 scans from 224 patients– 90 at 3T and 285 at 1.5T; 212 baseline (acute) MRIs, 105 MRIs performed immediately following iA-therapy, 12 MRIs performed 3-6 days post iA-therapy and 46 follow-up MRIs in patients who did not undergo iA-therapy. More than one MR examination was included for 141 patients: 2 with 4 scans (DEFUSE 2), 6 with 3 scans (DEFUSE 2) and 133 with 2 scans (110 from DEFUSE 2 and 23 from EPITHET). A single MR examination was included for 83 patients (28 from DEFUSE 2, 47 from SENSE 3 and 8 from EPITHET), who either did not undergo acute or follow-up imaging, or did not have PWI as a part of the follow-up MR. The order of the 375 MRs was randomized, to avoid recall bias arising from two MRs belonging to the same patient being presented successively.• *Diagnostic review:* An experienced neuroradiologist (blinded to whether the MRI was an acute, post DSA or follow-up study) performed the reads. GRE images were presented separately to the PWI images (at a separate sitting 2 weeks apart). GRE images for the first 181 randomized MR studies, and the PWI images for the remaining 194 MR studies (the reader also had access to the DWI images for each MRI) were read. After two weeks, to reduce the possibility of recall bias, PWI images from the first 181 MR studies, and GRE images from the other 194 MRIs (together with DWI images) were reviewed. The GRE and PWI images were rated for: image quality (1-3, good-poor); presence/absence of hemorrhage; age (acute or subacute *vs.* chronic) and type of hemorrhage (macro *vs.* micro; primary intra-parenchymal hemorrhage *vs*. hemorrhagic transformation [HT]; subarachnoid or intra-ventricular hemorrhage). The presence or absence of iA-thrombus was recorded. Lastly, the DSAs (the gold-standard for the presence of iA-thrombus) were reviewed, and the presence/absence of thrombus recorded. A DSA performed within 24 hours was available for 206 MRIs (203 DEFUSE 2 and 3 SENSE 3). The accuracy of GRE and PWI for the detection of intra-arterial thrombus was determined for these 206 MRIs. • *Data analysis*: The diagnostic sensitivity, specificity and accuracy of PWI for the detection of hemorrhage was determined using the findings on GRE as the *gold-standard*. False positive and false negative cases were reviewed by an experienced neuroradiologist (the entire MR study, and CT where available were reviewed). The sensitivity, specificity and accuracy for the detection of intra-arterial thrombus was determined for PWI and GRE, using the findings on DSA as the *gold-standard*.

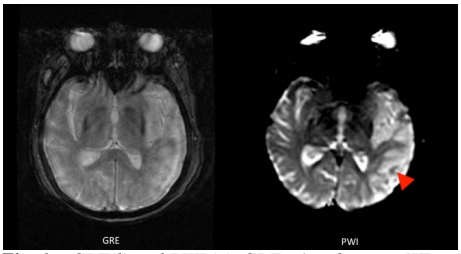

***Fig. 1** – GRE(l) and PWI (r). GRE missed macro HT.*

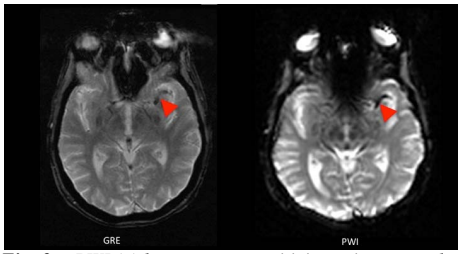

***Fig. 2** – PWI (r) has greater sensitivity to intravascular thrombus.*

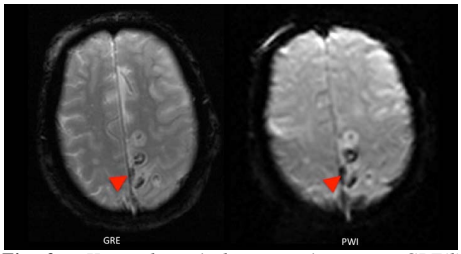

***Fig. 3** – Hemorrhage is less conspicuous on GRE(l) than PWI.*

RESULTS: GRE DSC PWI demonstrated a high sensitivity (93%), specificity (94%) and accuracy (94%) for the detection of intracranial hemorrhage. 10/71 micro-hemorrhages (3 acute and 7 chronic) were missed on PWI, but detected on GRE. Only 1 of 93 macro-hemorrhages (a small area of hyperacute hemorrhagic transformation of stroke) was missed on PWI. There were 12 "false positives" on PWI; after review of the full MR examination, and CT, in these 12 cases revealed that two of these were in fact true macrohemorrhages (**Fig. 1**), and 9 true microhemorrhages missed on GRE, with only one (!) real false positive. This highlighted the deficiency of GRE as the *gold-standard* for the detection of hemorrhage. Intravascular thrombus was detected with greater sensitivity by PWI (84% vs 79% for GRE) (**Fig. 2**). In most cases where intravascular thrombus was missed on PWI, this was due to the thrombosed vessel not being covered by the PWI slice stack. Difference in specificity for detection intra-arterial thrombus was minimal (91% for PWI *vs* 92% for GRE). PWI image quality was poorer than GRE in the EPITHET cohort, due to the fact that EPITHET has used more scanner from a previous generation which has usually poorer image quality. In DEFUSE 2 and especially in the newest dataset (SENSE 3), the quality of PWI was equivalent to GRE. Hemorrhage was noted by the reader to be frequently more conspicuous on PWI than GRE (**Fig. 3**).

DISCUSSION AND CONCLUSION: While previous studies have found that diffusion-weighted EPI is of insufficient sensitivity when compared to GRE for the detection of acute hemorrhage in AIS [3], the accuracy of PWI has not previously been examined. In this pooled study, we found that GRE-DSC-EPI based PWI has a high sensitivity and specificity for the detection of acute hemorrhage, and HT of acute stroke in particular. It's main failure is in the detection of small chronic microhemorrhages. However, these lesions do not influence the decision to perform thrombolysis for acute stroke [4]. Of note, PWI is superior to GRE for the detection of intra-arterial thrombus.

In conclusion, our findings support the exclusion of conventional GRE images from an acute stroke protocol. Hemorrhage screening can be performed adequately with the baseline images from GRE DSC PWI (i.e. the first few time points prior to contrast arrival).

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