Segmented 3D Echo Planar Acquisition for Rapid Susceptibility-Weighted Imaging: Application to Microhemorrhage Detection in Traumatic Brain Injury

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Background: Susceptibility-weighted imaging (SWI) provides superior image contrast of cerebral microhemorrhages (CMBs). It is based on a three-dimensional (3D) gradient echo (GRE) sequence with a relatively long imaging time.

Purpose: To evaluate whether an accelerated 3D segmented echo planar imaging SWI is comparable to GRE SWI in detecting CMBs in traumatic brain injury (TBI).

Study Type: Prospective.

Subjects: Four healthy volunteers and 46 consecutive subjects (38.0 ± 14.4 years, 16 females; 12 mild, 13 moderate, and 7 severe TBI).

Field Strength/Sequence: A 3 T scanner/3D gradient echo and 3D segmented echo planar imaging (segEPI).

Assessment: Brain images were acquired using GRE and segEPI in a single session (imaging time = 9 minutes 47 seconds and 1 minute 30 seconds, respectively). The signal-to-noise ratio (SNR) calculated from healthy volunteer thalamus and centrum semiovale were compared. CMBs were counted by three raters blinded to diagnostic information.

Statistical Tests: A t-test was used to assess SNR difference. Pearson correlation and Wilcoxon signed-rank test were performed using CMB counts. The intermethod agreement was evaluated using Bland–Altman method. Intermethod and intrarater reliabilities of image-based diffuse axonal injury (DAI) diagnoses were evaluated using Cohen’s kappa and percent agreement. P ≤ 0.05 was considered statistically significant.

Results: Thalamus SNRs were 16.9 ± 2.2 and 16.5 ± 3 for GRE and segEPI (P = 0.84), respectively. Centrum semiovale SNRs were 25.8 ± 4.6 and 21.1 ± 2.7 (P = 0.13). The correlation coefficient of CMBs was 0.93, and differences were not significant (P = 0.56–0.85). For DAI diagnoses, Cohen’s kappa was 0.62–0.84 and percent agreement was 85%–94%.

Data Conclusion: CMB counts on segEPI and GRE were highly correlated, and DAI diagnosis was made equally effectively. segEPI SWI can potentially replace GRE SWI in detecting TBI CMBs, especially when time constraints are critical.

Evidence Level: 1
Technical Efficacy: Stage 2

Traumatic brain injury (TBI) is a notable cause of morbidity and mortality worldwide, especially in children and young adults. In the United States, approximately 1.7 million people sustain a TBI annually, contributing to a third of all injury-related deaths. The prevalence of individuals with TBI-related long-term disability in the United States is approximately 3–5 million. Autopsy studies show that diffuse axonal injury (DAI) is a hallmark of moderate and severe TBI. DAI is typically accompanied by small blood breakdown products detectable on MRI as cerebral View this article online at wileyonlinelibrary.com. DOI: 10.1002/jmri.28326
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microhemorrhages or microbleeds (CMBs), which are regarded as a neuroimaging hallmark of TBI.³

CMBs consist of paramagnetic blood breakdown products, including deoxyhemoglobin, methemoglobin, and hemosiderin. The magnetic susceptibility of these paramagnetic substances differs from that of the surrounding, weakly diamagnetic, tissues.⁷ The difference in susceptibility induces local magnetic field inhomogeneities, which dephase neighboring nuclear spins resulting in phase accumulation and T₂* signal loss in MRI.¹⁰ Both effects are dependent largely on the strength of the magnetic field as well as the echo time of the sequence. The susceptibility-induced signal loss appears as small hypointense foci in T₂*-weighted images acquired using gradient recalled echo (GRE) pulse sequences.¹⁰

Three-dimensional (3D) susceptibility-weighted imaging (SWI) was introduced to further improve the detection of CMBs by employing image phase information.¹¹ This technique takes advantage of the difference in image phase accumulation to further enhance GRE image contrast.¹² By combining a long echo time with phase-based contrast enhancement, SWI increases the sensitivity of susceptibility effects and thus the detection of CMBs. Consequently, the sensitivity of SWI in detecting microhemorrhages is improved over GRE magnitude images,¹² and it is increasingly being used in assessing TBI.

While SWI provides superior image contrast of CMBs, its relatively long imaging time is a limiting factor for routine clinical use. At 3 T, an echo time (TE) of 20 msec or longer is typically employed to generate sufficient T₂* weighting¹³,¹⁴ and therefore requires a somewhat longer repetition time (TR). For GRE-based SWI, the combination of a single echo readout for each TR and the desire for relatively high spatial resolution leads to acquisition times typically in the range of 5–10 minutes,¹⁵,¹⁶ although shorter times are possible with limited brain coverage or reduced spatial resolution.¹⁴,¹⁷

The use of 3D multishot or segmented EPI (segEPI) has been proposed to accelerate SWI acquisition with satisfactory image quality.¹⁸ Such acceleration is particularly important if SWI is to be used for the assessment of TBI patients in acute settings, where shorter scan durations are desired for rapid assessment and to minimize patient discomfort.

Thus, the goal of this work was to determine how SWI generated from a segEPI pulse sequence (henceforth segEPI SWI) compares to traditional SWI generated from a GRE pulse sequence (henceforth GRE SWI), specifically in the context of TBI and the detection of traumatic CMBs.

Materials and Methods

Subjects

Two sets of subjects were used, one consisting of healthy volunteers for comparing image signal-to-noise ratio (SNR), and the other consisting of TBI patients for comparing CMB assessment and DAI diagnosis. The SNRs of GRE SWI and segEPI SWI were estimated from brain images of four healthy volunteers. Each of the volunteers signed a written informed consent to enroll in an institutional review board (IRB) approved protocol (ClinicalTrials.gov Identifier: NCT00001711). The CMB counting and subsequent analyses were performed on brain images acquired from 46 consecutive subjects (16 females and 30 males), enrolled in a longitudinal brain imaging study of TBI under an IRB approved protocol (ClinicalTrials.gov Identifier: NCT01132898). Each of them signed a written informed consent. The ages of the subjects ranged from 18 to 69 years with a mean age of 38.0 ± 14.4 (mean ± standard deviation) years. The severity of TBI was classified by physicians at the Clinical Center, NIH based on clinical history and criteria established by the Department of Defense and Veterans Affairs.¹⁹ Among the subjects, there were 14 non-TBI subjects, as well as 12 mild, 13 moderate, and 7 severe TBI subjects, representing 30.4%, 26.1%, 28.3%, and 15.2% of the subjects, respectively.

MRI Acquisitions

MR images were acquired from each patient in a single imaging session on a Siemens Biograph mMR 3 T MRI system (Siemens, Erlangen, Germany). In each patient, GRE SWI and segEPI data were obtained sequentially. For the GRE SWI, magnitude and phase images were obtained using the vendor-provided SWI sequence, which was a standard 3D GRE pulse sequence with first-order gradient moment nulling (GMN) flow compensation. Contrast parameters for the GRE SWI were TR = 40 msec, TE = 25 msec, flip angle = 15°, and bandwidth (BW) = 50 Hz/pixel. Geometric parameters were image matrix = 448 × 439 × 72, and voxel size = 0.5 × 0.5 × 2 mm. In addition, parallel imaging (GRAPPA) was used with an acceleration factor of 2. For 3D segEPI, a custom sequence was built from the vendor provided prototype 3D EPI sequence; flow compensation was not included. For the comparison with GRE SWI, contrast parameters of the segEPI SWI were TR 64 msec, TE 25 msec, flip angle 20°, BW 466 Hz/pixel. Geometric parameters were identical. Acceleration was provided by using an echo train length (ETL) of 15 and no parallel imaging. The imaging time of the segEPI SWI was 1 minute 30 seconds, as compared to 9 minutes 47 seconds for the GRE SWI, yielding an acceleration factor of approximately 6.5.

Signal-to-Noise Ratio

To measure the SNR of the 3D GRE and 3D segEPI images, two consecutive acquisitions of each sequence were performed in each healthy volunteer. SNRs were calculated over a region of interest (ROI) by using the dual-acquisition subtraction method:²⁰

\[
\text{SNR} = \frac{1}{\sqrt{2}} \frac{\text{mean}(I_1 + I_2)}{\text{std}(I_1 - I_2)} \bigg|_{\text{ROI}} = \sqrt{2} \frac{\text{mean}(I_1 + I_2)}{2 \text{std}(I_1 - I_2)} \bigg|_{\text{ROI}},
\]

where \(I_1\) and \(I_2\) denote the magnitude images of the two consecutive acquisitions, \(\text{mean}(\cdot)\bigg|_{\text{ROI}}\) and \(\text{std}(\cdot)\bigg|_{\text{ROI}}\) represent the average and standard deviation of image intensity over the ROI. After the brain images were rigidly co-registered using FMRIB’s linear image registration tools,²¹ two ROIs were manually taken on the image slice containing the largest area of thalamus or centrum semiovale: one on the left hemisphere and the other on the right hemisphere. SNR
values were calculated from the ROIs in each of the two brain regions.

**Image Analysis**

Brain images acquired using the two pulse sequences, 3D GRE and 3D segEPI, were sent to a clinical PACS system (Carestream Health, New York, USA) with minimum intensity projection (minIP) and image registration capabilities. To obtain phase-enhanced SWI, the Laplacian phase unwrapping algorithm was applied to the raw phase images, and the magnitude images were modulated using the filtered unwrapped phase images.\(^\text{22}\) Blinded review of images from each sequence was conducted independently by two neuroradiologists and an imaging researcher (J.A.B of 22 years of experience; I.P. 6 years; W.-T.W. 20 years), who counted the number of discrete hemorrhages detected within the whole 3D brain. Images were de-identified with the acquisition details removed so that the raters were unable to identify the scan type. To minimize bias, the 46 pairs of data sets were reviewed in two sessions separated by at least 2 weeks. In session 1, CMBs were counted by tagging them on a PACS workstation on exclusively either the GRE SWI or segEPI SWI images, randomly split 50% each, from each patient. In session 2, the remaining images were reviewed and tagged. To assist in the identification of CMBs, the magnitude, filtered phase, phase emphasized SWI and minIP of the datasets were made available. Finally, each patient was classified as DAI positive or negative based on the CMB count; a CMB count of four or more was considered DAI positive based on the NINDS Common Data Elements criteria.\(^\text{23}\)

**Statistical Analysis**

A paired \(t\)-test was performed to assess the null hypothesis that the average SNRs from the two acquisition methods (3D segEPI and 3D GRE) were equal. Given that 56% of the subjects were non-TBI or mild TBI, the CMB counts were highly skewed toward zero or low-value counts. In addition to this non-normality, outliers of the CMB counts were expected from the severe TBI patients. Therefore, the agreement between the ratings of the two acquisition methods was evaluated using a Wilcoxon signed-rank test to assess the null hypothesis that the CMB counts from the raters have equal mean signed rank. The agreement of the two methods was further analyzed using the Pearson correlation coefficient. The linear correlation coefficient of the CMB counts on GRE SWI and on segEPI SWI was calculated. Since the skewness of the CMB counts toward zero or low-value counts gives more weighting for high-value counts in the correlation analysis, a logarithmic transformation was applied to the CMB counts \((\geq 1)\) to improve the weighting distribution. Subsequently, Bland–Altman analyses were used to graphically assess the difference-average relation between the CMB counts from the two methods and the reference identity line. Computation of the bias, standard deviation, and 95% confidence interval, as well as generation of a Bland–Altman plot, were performed using GraphPad Prism 8 (GraphPad Software, CA, USA).

Clinically, the precise count of CMBs may be less important than the classification of the patient into the category of DAI based on the threshold of \(\geq 4\) CMBs. Therefore, further statistical analyses were based on the diagnoses of DAI by the raters’ CMB counts on the GRE and segEPI images. The intermethod and interrater

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**FIGURE 1:** Visualization of hemorrhages (arrows) was very similar on GRE SWI and segEPI SWI.

**FIGURE 2:** Comparison of CMB counts on segEPI SWI versus GRE SWI. Counts were averaged over the three raters, and logarithm normalized before linear regression.

**FIGURE 3:** Bland–Altman plot of Logarithm of CMB counts (black circles) compared to the reference unity line (black solid line). The solid blue line represents the mean difference 0.121, and the dashed blue lines the 95% confidence interval (−0.4 to 0.642).
The reliability of the DAI diagnosis were evaluated by Cohen’s kappa and percent agreement.²⁴ For all analyses, P values equal to or less than 0.05 were considered statistically significant.

Results

The SNR calculated from the two ROIs of 2334 ± 262 (mean ± standard deviation) voxels in total in the thalamus was 16.9 ± 2.2 for the GRE SWI and 16.5 ± 3 for the segEPI SWI (t-test, P = 0.84). The SNR calculated from the two ROIs of 6227 ± 1068 voxels in total in the centrum semiovale was 25.8 ± 4.6 for the GRE SWI and 21.1 ± 2.7 for the segEPI SWI (t-test, P = 0.13).

Visualization of CMBs on GRE SWI and segEPI SWI is shown in Fig. 1. Across all subjects, the CMB counts on GRE SWI averaged over the raters were 12.6 ± 35.2 (mean ± standard deviation) with a range from 0 to 177.6 and a median of 1.3. For GRE SWI, Wilcoxon signed-rank tests indicated that there was no significant difference in median CMB counts between raters 1 and 2 (P = 0.71), raters 1 and 3 (P = 0.60), as well as raters 2 and 3 (P = 0.18). The P values of Wilcoxon signed-rank tests of CMB counts on GRE and segEPI were 0.77, 0.56, and 0.85 for the raters 1–3, respectively.

In Fig. 2, the Pearson correlation analysis of CMB counts on segEPI SWI averaged over the raters and those on GRE SWI images showed that they were highly correlated with a correlation coefficient of 0.93. The slope of the fitted line was 0.97 ± 0.09 with the reference identity line lying within its 95% confidence intervals. The Bland–Altman plot of the CMB counts and the reference identity line is shown in Fig. 3, exhibiting a bias of 0.121 and standard deviation of 0.266.

The agreement of the DAI diagnosis across methods by each rater (within rater) is shown in Table 1. The corresponding kappa and percent agreement were 0.73–0.84 and 91%–94%, respectively, as listed in Table 2. To see whether the difference in agreement was rater dependent, we generated contingency tables for the agreement of DAI diagnoses across raters within method, as shown in Table 3. Table 4 shows that, for DAI diagnosis agreements based on GRE SWI, the corresponding kappa and percent agreement were in the range of 0.62–0.76, and 85%–91% respectively. For DAI diagnosis agreements based on...
segEPI SWI, the ranges were 0.72–0.88, and 91%–96%, respectively.

Discussion
In this work, a highly accelerated 3D segEPI SWI was compared with a conventional 3D GRE SWI in terms of image SNR, CMB count, and DAI diagnosis. We found that the segEPI SWI provided comparable SNR, highly correlated CMB counts, and good/moderate to substantial agreement in DAI diagnosis, while greatly reducing acquisition time.

When comparing T2* -weighted sequences, it is important to use the same echo time so that T2* contrast would be similar. In this work, with the 15-echo train, segEPI BW was increased so that its TE matched with TE in GRE. This resulted in a 60% longer TR for the segEPI vs. GRE, which partially offset the acceleration gained by the use of the echo train. The longer TR alters contrast slightly, most notably in the contrast between CSF and brain parenchyma; we partially compensated for this by adjusting the flip angle. Even with the longer TR, the 3D segEPI achieved a 6.5-fold acceleration to cover the whole brain in 1.5 minutes, which is shorter than the aforementioned typical 5-to-10-minute SWI imaging time. While the accelerated imaging was achieved at a cost of a mild reduction in SNR, it reduced the effects of patient motion, including ghosting artifacts in magnitude images and unreliable phase images.

It is known that EPI readouts result in image blurring due to k-space T2* modulation and image distortion due to resonance offsets from susceptibility-induced field inhomogeneity. However, in this study, the use of the relatively short echo train of 15 echoes did not impede the ability to generate high-resolution images that accurately depicted CMBs, similar to the experience in using segEPI to demonstrate central veins in MS. Imaging time can be further reduced by increasing the ETL, but there will be a concurrent increase in image degradation, particularly in regions with field inhomogeneity, for example, near the skull base. Note that two of the regions, the basal forebrain and anterior temporal lobe, are common sites of hemorrhagic contusions following TBI. Slight image blurring and distortion in these two regions may reduce sensitivity to microhemorrhages.

Although the CMB counts from the two acquisition methods were highly correlated and had the same mean signed rank, the slope of the best fit line was less than one, suggesting that CMB counts from 3D segEPI may be fewer than those from 3D GRE. The use of flow compensation (first-order GMN) for effects of blood flows with constant velocities could potentially affect conspicuity of CMBs, which may have affected the CMB counts. In this work, flow compensation was applied during the 3D GRE acquisition, but it was not available for the 3D segEPI sequence. Lack of flow compensation on the 3D segEPI sequence results in signal loss throughout the cerebral arteries leading to a uniformly dark appearance of the arteries, similar to the veins and hemorrhages. In contrast, the flow compensated 3D GRE at least partially compensates for flow-related signal loss, so that arteries do not appear dark except in regions where complex flows (e.g., turbulent flow, vortex flow, pulsation, or other types of flow acceleration that result in nonconstant velocities) exist. One can speculate that in the absence of complex flow the flow compensation of the 3D GRE sequence might improve visualization of CMBs, whereas in the presence of complex flows, the complete visualization of arteries using 3D segEPI would be more beneficial. The first-order GMN compensates the effects of blood flows with constant velocities, reducing signal loss and correcting ghosting artifacts originating from laminar and plug flows with constant flow rates. However, uncompensated effects of blood flow acceleration, pulsation, and higher-order motions can lead to hypointense segments; in TBI, these segments can mimic microhemorrhages.

Limitations
Our analysis was at the patient/image level, not at the individual CMB level. We did not perform a direct comparison of the conspicuity of each individual CMB between the two pulse sequences. It is possible that such an analysis would reveal more differences in the utility of the two techniques. Another limitation was in the ability of the reviewers to accurately count CMBs when the count was very high. CMBs in the context of trauma often line up along parenchymal veins, potentially to the extent that individual hemorrhages are difficult to distinguish. Because there is no reference standard or pathologic proof in this study, it is impossible to completely exclude the presence of artefactual microhemorrhages leading to an inaccurate microhemorrhage count.

Other approaches to accelerate image acquisition, for example, SENSE, GRAPPA, CAIPIRINHA that can be applied to 3D GRE acquisitions sequences depend on the number of individual coil elements and provide acceleration factors typically in the range of 2–4, potentially more than 10 when combining multiple techniques. The combined acceleration factor may be close to the acceleration provided by the echo train in segEPI, which was 15 in this work. Furthermore, these methods are theoretically compatible with the 3D segEPI sequences, potentially allowing for further acceleration and only limited by the available SNR.

Given the sample size and the lack of perfect concordance between observers, there are limitations to how small a difference this study could detect. Post hoc power analysis shows that this study was powered to detect a 25% change in slope from identity with 80% power. Because of this, we cannot exclude small differences between the techniques. To reach this power we needed nearly 50 subjects; it is not clear...
that the population size needed to make a finer distinction would be useful. Another limitation is that we only tested the image quality for a specific set of parameters. It may be the case that one sequence is more fragile with respect to parameter variations than the other, for example, distortions may become much worse with longer echo train lengths. Our choices of parameters for the segEPI pulse sequence were selected to mimic the performance of the manufacturer’s product GRE sequence without extensive optimization.

Conclusion
Accelerated acquisition using a 3D segEPI pulse sequence can substantially reduce imaging time for SWI with limited degradation of image quality, and little or no loss in the ability to detect hemorrhages. For an MRI exam in the acute management of TBI where time is of the essence, use of the 3D segEPI sequence can offer a potential advantage.

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