Arrival Time Correction for Dynamic Susceptibility Contrast MR Permeability Imaging in Stroke Patients

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Abstract

Purpose: To determine if applying an arrival time correction (ATC) to dynamic susceptibility contrast (DSC) based permeability imaging will improve its ability to identify contrast leakage in stroke patients for whom the shape of the measured curve may be very different due to hypoperfusion.

Materials and Methods: A technique described in brain tumor patients was adapted to incorporate a correction for delayed contrast delivery due to perfusion deficits. This technique was applied to the MRIs of 9 stroke patients known to have blood-brain barrier (BBB) disruption on T1 post contrast imaging. Regions of BBB damage were compared with normal tissue from the contralateral hemisphere. Receiver operating characteristic (ROC) analysis was performed to compare the detection of BBB damage before and after ATC.

Results: ATC improved the area under the curve (AUC) of the ROC from 0.53 to 0.70. The sensitivity improved from 0.51 to 0.67 and the specificity improved from 0.57 to 0.66. Visual inspection of the ROC curve revealed that the performance of the uncorrected analysis was worse than random guess at some thresholds.

Conclusions: The ability of DSC permeability imaging to identify contrast enhancing tissue in stroke patients improved considerably when an ATC was applied. Using DSC permeability imaging in stroke patients without an ATC may lead to false identification of BBB disruption.

Introduction

Magnetic resonance imaging (MRI) of the blood-brain barrier (BBB) can be achieved using dynamic contrast enhanced (DCE) T1-weighted imaging. This methodology has been well described [1] and involves calculation of a measure of permeability, \( K_{\text{trans}} \). Although DCE MRI has been shown to be a robust research tool, it has yet to become part of standard clinical practice. In part this is due to the time-consuming process of acquiring the images required for generating permeability measures with DCE MRI.

Conversely, dynamic susceptibility contrast (DSC) MRI is a routinely acquired imaging technique most commonly used in ischemic stroke patients or brain tumor patients. In brain tumor patients DSC MRI is used to measure cerebral blood volume (CBV) of the tumor as this has been associated with tumor grade [2]. However, leakage of contrast due to BBB disruption can lead to an underestimation of CBV [3]. A method for contrast leakage has been described [4] and applied to brain tumor patients [3]. In order to correct for BBB disruption, a measure of permeability is extracted from the DSC MRI acquisition. This approach generates a measure that has been labeled \( K_2 \) which is an estimate of \( K_{\text{trans}} \). DSC MRI is routinely collected on acute stroke patients at many large academic medical centers as part of the evaluation for treatment [5]. In this setting it is referred to as perfusion weighted imaging (PWI) and provides information about the blood flow to the brain. Several groups have attempted to extract permeability information from PWI in stroke [6–8]. However, the approach used in the brain tumor literature, which assumes symmetric perfusion of the brain, can be subject to error when applied to patients with perfusion deficits, such as acute stroke patients. The delay in contrast delivery to areas of hypoperfusion makes calculation of \( K_2 \) inaccurate. Thus we developed a technique that applies an arrival time correction (ATC) prior to calculation of \( K_2 \). The purpose of this study was to compare \( K_2 \) measurements made with and without ATC in a population of stroke patients who were known to have damage to the BBB based on T1-post contrast imaging.

Materials and Methods

DSC MR Permeability Imaging

There are several approaches to using DSC MRI to assess the permeability of the BBB that have been described in the literature [3,4,6–8]. However, none of these techniques perform an ATC. We chose the method described by Boxerman et al. to use as the
uncorrected method of DSC MRI permeability imaging. This technique has been described in detail elsewhere [3] but will be briefly summarized here.

Changes in tissue contrast agent concentration are measured as changes in relaxivity with the equation [4]:

$$\Delta R2(t) = \frac{-1}{TE} \ln \left( \frac{S(t)}{S_0} \right)$$  

(1)

Where $TE$ is the time to echo, $S(t)$ is the signal intensity in the voxel at time $t$, and $S_0$ is the baseline signal intensity prior to delivery of the contrast bolus. When contrast leaks through the BBB into the parenchyma the measured signal is more accurately characterized by adding a term to equation (1) to account for BBB effects [4]:

$$\Delta R2(t)_{\text{measured}} = \Delta R2(t) - \frac{TR(\frac{TE}{TR})}{TE(1 - e^{-\frac{TR}{TE}})} R_1 C_{\text{tissue}}(t)$$  

(2)

Where $TR$ is the time to repetition, $R_1 = \frac{1}{T1}$ and $C_{\text{tissue}}(t)$ is the concentration of contrast in the tissue at time $t$. The amount of contrast leakage for each voxel is estimated by assuming that the measured relaxivity change is a linear combination of the average signal in non-enhancing voxels and some fraction of its time integral:

$$\Delta R2(t) = K_1 \Delta R2^c(t) - K_2 \int_0^t \Delta R2(t')dt'$$  

(3)

Where $\Delta R2^c(t)$ is the measured, uncorrected change in relaxivity, $\Delta R2^c(t)$ is the average signal for a region of non-enhancing voxels, and $\int_0^t \Delta R2(t')dt'$ is the integral of the average signal for a region of non-enhancing voxels which is essentially the average cerebral blood volume (CBV). The term $K_1 \Delta R2^c(t)$ represents the uncontaminated portion of the measured signal as the average signal of non-enhancing values times a scaling factor $K_1$. The $K_2 \int_0^t \Delta R2(t')dt'$ term reflects the effect due to leakage and is represented as the average CBV of non-enhancing tissue times $K_2$ where $K_2$ is a fraction between 0 and 1. Thus when equation 3 is solved for $K_2$, the fraction of the average CBV that has leaked at each voxel is approximated.

Arrival Time Correction

Inherent in the MRI DSC permeability imaging technique described above is the assumption that the recorded signal for a given voxel can be represented as a scaled version of the average signal. For example, if a voxel had no contrast leakage, $K_2$ would be zero and equation 3 would become:

$$\Delta R2(t) = K_1 \Delta R2^c(t)$$  

(4)

However, this assumption fails when there is a delay in contrast delivery such as in a perfusion deficit of a stroke patient. The shape of the measured curve is often very different in hypoperfused tissues. As the curve becomes broader, it peaks later and has a different area underneath it. Thus our approach to performing an ATC was to adjust $\Delta R2(t)$ on a voxel by voxel basis such that it best fits the true morphology of the recorded signal. We defined a term:

$$\Delta R2^c(t)_{\text{ATC}} = \gamma \Delta R2(t)^{\frac{1}{\alpha} + \tau}$$  

(5)

Where $\Delta R2^c(t)_{\text{ATC}}$ is the average signal after ATC, $\gamma$ is a magnitude scaling factor, $\alpha$ is a time scaling factor, and $\tau$ is a time offset. Thus equation 3 becomes:

$$\Delta R2(t) = \Delta R2^c(t)_{\text{ATC}} - K_2 \int_0^t \Delta R2^c(t')_{\text{ATC}}dt'$$  

(6)

where $K_1$ is dropped because scaling has been performed as part of the ATC. Using a multiple least-squares approach, the values for $\gamma$, $\alpha$ and $\tau$ are determined by minimizing the following equation over a range of values:

$$\min{\sqrt{(\Delta R2^c(t)_{\text{ATC}})^2 - (\Delta R2(t))^2}}$$  

(7)

Thus, at every voxel $\gamma$, $\alpha$ and $\tau$ are determined to create an ATC non-enhancing curve to compare with the recorded signal to determine if there is evidence of BBB disruption. The $K_2$ value generated again represents the fraction of the CBV that has leaked. However, in this case, the $K_2$ value is the fraction of the CBV calculated using the corrected concentration curve. An example of the $K_2$ values before and after ATC is shown in Figure 1. An example of how the non-enhancing curve is adjusted with the ATC is shown in Figure 2.

Patient Selection

This study was approved by the Johns Hopkins Institutional Review Board and did not require consent. Consent was not required by our IRB for this de-identified database due to the retrospective nature of the study and the lack of patient interaction. MRIs of all patients admitted to our stroke service over the time period from 8/1/2010-3/31/2011 were retrospectively reviewed by one author to identify evidence of BBB disruption characterized by enhancement on T1 post-contrast (T1PC) images. Two other authors blinded to whether patients had been identified as having BBB disruption reviewed a collection of patients with and without BBB disruption and independently determined if they had evidence of enhancement on T1 post-contrast (T1PC) images. There was agreement between all three authors on all patients included in the study except for one patient for whom only two reviewers identified BBB damage. However, since the official radiology report for the scan in question commented on the presence of enhancement on T1 post-contrast (T1PC) images, this patient was included in the study. Patients with BBB disruption, a successful DSC MRI scan, and an acute stroke on diffusion weighted imaging (DWI) were included in the analysis. If a patient had more than one MRI done during their hospital stay that met the inclusion criteria, then all eligible scans were included. Posterior circulation strokes were excluded due to potential artifacts in perfusion imaging at the base of the skull. Patients with evidence of hemorrhagic transformation on perfusion source images were excluded due to the artifact caused by hemosiderin deposition on gradient-echo echo-planar images.
Image Acquisition

Images were acquired as part of routine clinical care; thus there was no standardization of imaging parameters. Our institution has several MRI scanners with magnet strengths ranging from 1.5–3 Tesla. Siemens, Philips and General Electric brand scanners were used. Although the protocols varied, all patients included in the analysis had serial echoplanar gradient-echo images acquired prior to and during the injection of a weight-based dose of gadopentetate dimeglumine (Magnevist; Bayer HealthCare Pharmaceuticals). T1 weighted imaging was performed after the perfusion acquisition.

Image Processing

All image analysis was done with Matlab (Mathworks, Natick, MA, USA). $K_2$ images were generated from DSC images as described above. Using T1 post contrast images as a guide, regions of interest (ROI) were outlined in the ischemic hemisphere to delineate BBB disruption on the DSC source images. This was done visually by bringing up the T1 post contrast images next to the T2* baseline DSC source images. The ROI was then flipped into the contralateral hemisphere to create a control ROI.

Figure 1. The top row of images show a stroke on DWI/ADC which has some enhancement on post contrast T1 imaging. The bottom row shows the perfusion deficit on a TTP map, the permeability image when not corrected for arrival time, and the permeability image after arrival time correction. The green circles show corresponding areas of contrast leakage on the T1 post contrast and ATC permeability images. (DWI = diffusion weighted image, ADC = apparent diffusion coefficient, PWI = perfusion weighted image, TTP = time to peak, ATC = arrival time corrected).

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Receiver Operating Characteristic (ROC) Analysis

Voxels in the ROI of the ischemic hemisphere were designated as having BBB disruption, while voxels from the control ROI were designated as no BBB disruption. $K_2$ values are calculated in the permeability analysis as a fraction of the CBV, thus they range from 0 to 1. Using the $K_2$ values from the permeability analysis, voxels can be divided into 2 groups based on a threshold which is varied from 0 to 1. For instance, a threshold of 0.2 would indicate that 20% of the CBV would have to be measured as leakage on the $K_2$ image in order for it to be considered as representative of true BBB disruption. For every given threshold the classification of voxels as having BBB damage or not will result in true positives, false positives, true negatives and false negatives. Thus for every threshold a sensitivity and specificity is generated for both the corrected and uncorrected permeability images. Plotting sensitivity versus 1-specificity results in an ROC curve. A perfect test would result in a curve that intersects the top left hand corner. This would indicate that a threshold was identified that has a sensitivity of 1 and a specificity of 1. The ROC curve for a random guess results in a diagonal line from bottom left to top right. The area under the curve (AUC) is a measure of the overall performance of the test. For a perfect test the AUC would be 1 while the AUC for a random guess curve would be 0.5. ROC curves were generated to compare the performance of the uncorrected versus uncorrected images at identifying BBB damage.

Discussion

We set out to determine whether applying an arrival time correction (ATC) improves the ability of perfusion-weighted imaging to detect breakdown of blood-brain barrier following stroke. Our study confirms that DSC permeability imaging is improved using this correction. How does our finding impact on current approaches to imaging in acute stroke patients?

The role of BBB disruption in stroke patients has been investigated by a variety of measurement techniques [6,7,9–14]. These studies are driven by the idea that damage to the BBB in acute stroke patients may predict response to treatment. More specifically, damage to the BBB may provide a measure of the risk of intracranial hemorrhage (ICH), which is the most serious complication of thrombolytic stroke treatment. T1 post contrast imaging is the most commonly used clinical method for detecting damage to the BBB. It has been shown to be very specific for predicting ICH in stroke patients but not very sensitive [12]. FLAIR post contrast imaging, referred to as hyperintense acute reperfusion marker (HARM), has also been investigated and has been shown to predict hemorrhagic transformation and poor outcome in stroke patients [14]. However, this approach requires a delay between the administration of contrast and image acquisi-
into clinical use [5]. This body of literature, permeability imaging has not found its way approaches uses an ATC prior to calculating permeability. Despite investigated using various approaches [6–8], but none of these minutes. The use of DSC MRI to detect BBB has also been management of acute stroke, which takes place on the order of tion on the order of hours and thus is not practical for parenchyma, thus application of this technique requires knowledge of the underlying structures.

Despite its limitations, this study serves to describe a technique for ATC of DSC MRI permeability imaging which can be further tested in subsequent studies.

**Author Contributions**

Conceived and designed the experiments: RL PBB. Analyzed the data: RL SSJ DDV. Contributed reagents/materials/analysis tools: AEH. Wrote the paper: RL.

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**Figure 3.** The receiver-operator characteristic (ROC) curves, which demonstrate the ability to correctly identify enhancing tissue, are plotted before and after arrival time correction (ATC). Prior to correction the technique performs worse than random chance at some thresholds due to perfusion deficits. doi:10.1371/journal.pone.0052656.g003