INVESTIGATING ABSOLUTE QUANTIFICATION IN MR PERFUSION STUDIES: THE ROLE OF PARTIAL-VOLUME ERRORS

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INTRODUCTION

Ischemic stroke, a major cause of disability and mortality in Canada,[1] is an acute cerebral vascular accident that can generate permanent tissue damage due to reduction in blood supplied to brain tissue. The effects of stroke depend on the size and the location of the tissue damage. Computer tomography (CT) and magnetic resonance (MR) currently play an important role in diagnosing acute stroke by identifying the cause, determining the severity of the damage, and assessing effectiveness of potential treatments. Reversing the cause of the flow reduction and stabilizing the neurological condition are the key aims of stroke management.

Thrombolytic therapies are now available and in some patients, can restore the blood supply to the affected tissue. It has been shown that attempting treatment when either the tissue ischemic state or the time between stroke onset and treatment are not favorable can lead to further tissue damage.[2] Thus, therapies must be specifically applied only to patients who will benefit from them. One indicator of whether or not brain tissue is likely to become compromised is the cerebral blood flow (CBF). CBF is strongly related to the cellular metabolic condition (tissue ischemic state). MR-based perfusion protocols can provide relative (compared to normal tissue) CBF values but absolute quantification is not yet possible.

A major limitation to achieving absolute quantification is the presence of partial-volume errors (PVE) [3] that lead to poor accuracy and reproducibility of perfusion estimates. Various attempts to reduce partial-volume errors have included acquisition of an extra slice perpendicular to main arteries,[4] analysis of the complex MR signal,[5] and post-acquisition signal scaling.[6] Nevertheless, there remains a need for robust correction algorithms that apply to the majority of clinical scenarios. Here, we first explain the concept of PVE and its effect on MR perfusion estimates. We then describe a post-acquisition algorithm implemented to reduce partial-volume errors by improving the image resolution. We also introduce an at acquisition method for estimating partial-volume using principles from phase-contrast imaging.

PARTIAL-VOLUME ERRORS IN PERFUSION

To estimate cerebral flow values in MR perfusion studies, the signal from the artery feeding the tissue must be determined. Better characterization of this signal leads to more accurate flow values. This signal is usually obtained from an image voxel in or, more likely, including an artery. It has been suggested that voxels with very large blood volume should not be used for perfusion estimates [7] and, instead, that the arterial signal should be measured as near to the tissue-of-interest as possible, in order to minimize dispersion effects [8]. Thus, voxels lying on the larger cerebral arteries such as the middle cerebral artery (MCA) are most commonly used. Currently in MR perfusion imaging, the size of these preferred arteries are similar or smaller to the size of the imaging voxel. Therefore, more than one tissue type will be present in the selected voxel. The measured signal intensity from that voxel will equal the weighted average of each component; a condition known as volume averaging or partial voluming. PVE are considered a major limitation in absolute perfusion quantification.[3, 4, 9]

The fraction of the voxel volume occupied by the artery is the arterial-fractional volume (α). An α value of 1 is desirable since it means that the signal from that voxel is only from an artery. However, in practice different artery-containing voxels will have different and unknown α values due to the variation of the arterial diameter and location varying from patient to patient and from scan to scan.

In the perfusion imaging protocol used at our centre, oblique-axial images were acquired with a single-shot echo-planar imaging (EPI) technique with an acquisition matrix of 144 × 144, a field-of-view (FOV) of 24 cm × 24 cm, and a slice thickness of 5.0 mm. This results in 1.7 mm x 1.7 mm x 5.0 mm voxel (in the *x*, *y* and *z* directions). In addition, in perfusion imaging, the MCA that is used to measure the arterial signal is assumed to run parallel to and within the 5-mm thick slice. Depending on the MCA diameter (typically between 2 mm and 4 mm) and its orientation and position in the 5-mm slice, the arterial-fractional volume can range between 0.20 and 0.85 [9]. In Fig 1 all possible partial-volume levels are plotted for a 3-mm diameter MCA (assumed to be running parallel to *x*),

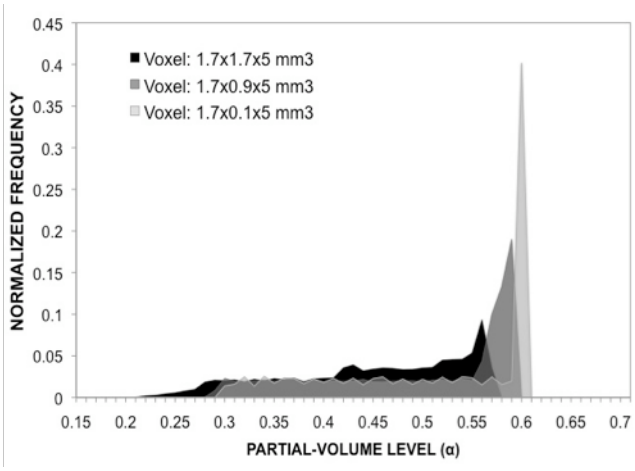

Figure 1: Normalized distributions of the partial-volume levels for a voxel of 1.7x1.7x5 mm^3 (black) allowing a random displacement in any direction of a 3 mm vessel. Smaller voxel sizes with changes in only 1 dimension, lead to L-shaped distributions (gray) shifted towards higher α values.

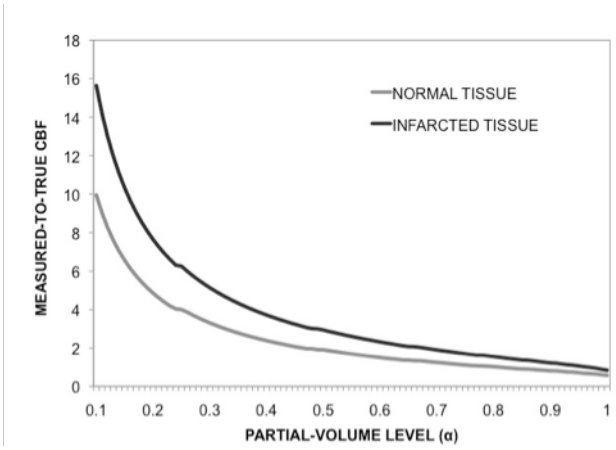

Figure 2: Cerebral blood flow estimates in the presence of partial-volume errors. The bias in the estimates is not linearly related to the α value and depends on the tissue type.

randomly displaced within the voxel in the *y* and *z* directions (1.7 mm × 5.0 mm). The simulation result is a broad, skewed distribution (black curve, Fig 1) with a median α value of 0.46. The high distribution peak at α = 0.56 shows that small displacements of the vessel from the centre of the voxel lead to similar α values; this observation is to be expected when the slice thickness is bigger than the vessel diameter. The low α values occur when the vessel is displaced towards the corners of the voxel. The small peak at $\alpha \approx 0.42$ is related to the geometry of voxel and vessel: as the vessel is fully displaced in the *y* direction it can be varied in *z* with little impact on α.

Using simulations, the fractional error in the CBF estimates at different α values was previously studied [9]. In Fig 2, this error is plotted as a function of the partial-volume error. An overall overestimate of the flow value is associated with PVE. This overestimation is non-linear and decreases as α increases. CBF estimates are, thus, highly variable and also highly dependant on the amount of partial voluming in the voxel(s) used to estimate the arterial signal. The flow estimates are also tissue dependent with a bigger error found in ischemic tissue; unfortunately this is precisely tissue that stroke treatment is targeting.

The average fractional error in CBF can be calculated in order to characterize performance. The average error is obtained by calculating the sum of the flow error (Fig 2) weighted by the probability function of the distribution for all possible partial-volume levels (Fig 1). For a 3-mm vessel in a 1.7 mm × 5.0 mm voxel (y-z directions), the average CBF overestimation is 220% for normal tissue and 350% for infarcted tissue. These estimates are consistent with the results described in [10] and used to obtained absolute perfusion values.

From the average error analysis, it is clear, that a measurement of the partial-volume level in the arterial voxel is needed. With a reliable α value estimate then correction of the perfusion parameters might be possible. If α measurement is not possible, imaging techniques should be designed to avoid or minimize PVE.

REDUCING PVE

In MR perfusion image, spatial resolution is compromised to obtain acceptable temporal resolution of the dynamic process as the bolus of contrast material travels through the brain. In addition the clinical need for full brain coverage suggests a minimum voxel volume on the order of 1.7 × 1.7 × 5.0 mm^3. For the proximal portion of the MCA that runs within the 5-mm slice this voxel volume results in PVE, hence the need to improve the image resolution.

We implemented the transient-error reconstruction algorithm (TERA) [11, 12] and used it as a post-acquisition technique to enhance the resolution of the MR image. Our goal was to improve the in-plane image resolution by extrapolating high-frequency components of the k-space (or Fourier space) data that were not collected. The k-space data was modeled using an auto-regressive (AR) moving-average (MA) model, and then extrapolated to a higher resolution. In Fig 3 the effects of applying TERA in the *y* direction (*i.e.*, phase-encode direction) to a phantom image are compared to those of FT image reconstruction with no extrapolation (zero padding). Ringing artifact ("Gibbs effects") due to truncation of the k-space is evident in the FT reconstructed image. In contrast, this artifact is

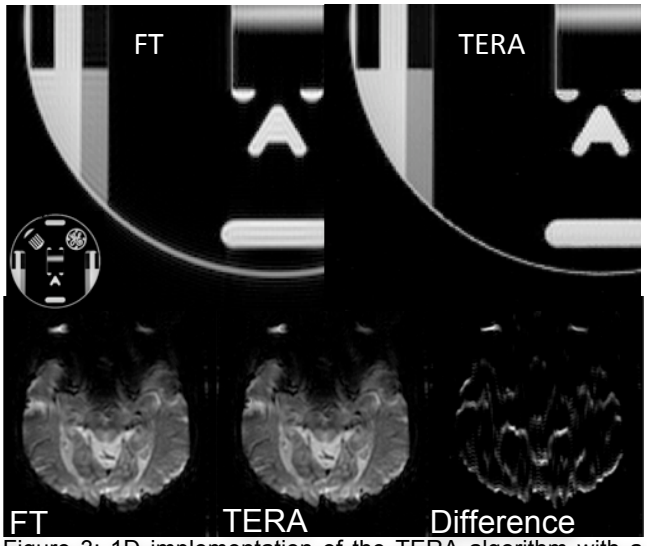

Figure 3: 1D implementation of the TERA algorithm with a fixed model order (p=30) in the *y* (vertical or anterior-posterior) direction. Less ringing effects are present in the TERA-based phantom image compared to the FT-reconstructed image. In the clinical example the effect of the TERA algorithm is less evident. Window for the difference image is 10% that of the FT or TERA images.

less evident in the TERA-based image. The level of artifact reduction depends on the order of the AR model (*p*) being used. Low orders ($1 < p < 10$) do not generate images with further improvement compared to the FT-based images. High orders ($p > 35$) leads to over-fitting of the model that produces high-intensity spikes in the final images. In addition, since the low-frequency collected data with a high signal-to-noise ratio, are used to fit the ARMA model and extrapolate k-space, a reduction of the final image noise is also expected. The ringing artifact reduction is more difficult to appreciate in the clinical image; however some recovery in the high frequency range can be seen from the difference image in the *y* (vertical) direction. Since our research to date illustrates some potential, applying TERA to clinical images and assessing their impact on arterial signal estimates need to be explored further

Simulation results of the effect of enhancing the image resolution on the partial-volume estimate are presented in Fig 1. In these simulations only the *y* direction (anterior-posterior) of the axial image was modified. The resolution in the x direction was fixed at 1.7 mm. MCA vessel diameter changes does not significantly affect the estimate of the partial-volume level. The shape of the distribution tends towards a "L"-shaped curve. The high peak indicates that we are more likely to estimate the same α value independently of the vessel position within the voxel. The average fractional CBF error is 200% and 310% for a voxel size of $1.7 \times 0.9 \times 5.0$ mm^3 and 190% and 300% for a $1.7 \times 0.1 \times 5.0$ mm^3 for normal and ischemic tissue respectively. A slight change in the fractional error can be expected from the displacement of the α distribution towards higher values (Fig 2). Still, for the current imaging protocol, the slice thickness contributes the most to PVE. A 5-mm slice thickness is required to guarantee coverage of the full brain. Reducing the slice thickness will also compromise the SNR as a smaller volume of tissue contributes to the collected signal. For a 3-mm slice thickness, a theoretical reduction of the average error in the CBF estimates of 40% for both normal and ischemic tissues types would be possible.

MEASURING PVE

The MR image intensity in a particular voxel depends on the entire content of the corresponding anatomical volume and the imaging sequence. In the presence of PVE, the signal intensity is a combination of the contributions of different tissues and does not characterize a single tissue type. To obtain an improved estimate of the arterial signal, a method of differentiating the signal intensity of the arterial component from that of surrounding brain tissue is needed. We have studied a method to estimate the partial-volume level in a voxel by selectively suppressing the signal from the arterial component using principles of phase-contrast (PC) imaging.

We have developed a modified MR perfusion sequence in which a symmetrical trapezoidal bipolar gradient was added in the frequency-encode direction (known as velocity suppressed (vs) EPI, abbreviated as vsEPI). With bipolar gradients, the phase of the acquired MR data becomes sensitized to moving spins, such as those in flowing blood [13]. Since phase is uniquely defined only over the $-\pi$ to π range, the maximum velocity that can be unambiguously encoded without phase-wrap (aliasing) is limited [14]. In a voxel containing spins flowing with a distribution of velocities, different levels of phase aliasing are present for the velocity values at specific sensitivities. This incoherence in the phase of the MR signal leads to signal voids from moving spins. Under the condition of complete intra-voxel dephasing, the measured signal results only from the static brain tissue within the voxel and can therefore be an indirect estimate of the arterial partial-volume level.

In Fig 4, the results from a healthy-volunteer scan using the vsEPI sequence are presented for regions-of-interest (ROI) in different tissue types. Images were acquired at 7 different velocity-sensitivities and an 8th acquisition was acquired without any velocity-sensitivity. For each of the velocity-sensitivity values, 20 temporal phases were collected with the vs gradients turned on and 20 phases with the vs gradients

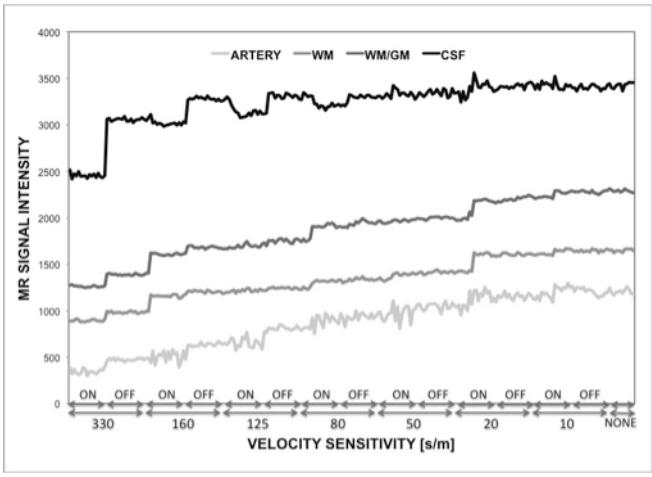

Figure 4: The MR signal intensity for different tissue types a several levels of velocity-sensitivity applied to the right/left direction of the patient. Increasing levels of sensitivity are associated with increasing level of intra-voxel dephasing within the moving spins. WM: white matter, GM: grey matter.

turned off. While the gradients are turned off the MR signal intensity escalates from a small value at a high sensitivity to a high value in the signal intensity when no gradients were used. This is due to an increment of the echo time that is needed to accommodate the bi-polar velocity-sensitivity gradients.

A voxel with only parenchyma tissue (GM/WM and WM in Fig 4) should not be affected by the bipolar gradients. The signal loss present at the two highest level of velocity-sensitivity for these tissues is assumed related to suppression of the signal at a diffusion level. The cerebrospinal fluid (CSF) flows with a velocity of 2 cm/s and the signal response in Fig 4 is as expected. We expect the arterial signal to show a reduction in the intensity level at the velocity-sensitivities presented in Fig 4. However, this reduction is not evident. Assuming complete intra-voxel dephasing in the MCA voxel, the estimated α values for the signals of Fig 4 ranged between 0.2 and 0.6; depending on the velocity-sensitivity level used. These α values are within the normal range for an MCA of approximately 3.2 mm in diameter as measured from the time-of-flight images. However, they also showed a dependency on the tissue ROI used. Considering the anatomical disposition of the MCA, using a ROI with a mixture of white and grey matter might generate more accurate α values.

SUMMARY

MR imaging is evolving from generating *qualitative* information that assists in differentiating normal from abnormal tissues to providing *quantitative* information characterizing specific processes in the body. In this research, we have demonstrated the potential of reducing partial volume errors using the TERA algorithm in EPI data. We discovered that the error correction needs further refinement in order to have a larger impact on the quality of the perfusion estimates. Given that using TERA in this way does not target the largest source of PVE, we chose to measure the partial volume levels in the voxels as a complementary method for improving the perfusion estimates. PC principles seem possible for measuring the partial volume levels. In this case, we need more analysis and investigation to confirm that this technique will be robust enough to apply confidently in clinical situations.

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