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Application of FT-based MMSE Deconvolution Method for Cerebral Blood Flow Measurement in Patients with Leukoaraiosis

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Abstract

Introduction—The bolus tracking (BT) technique is the most popular PW DSC-MRI method used for estimating CBF, CBV and MTT. The BT technique uses a convolution model that establishes the input-output relationship between blood flow and the vascular tracer concentration. SVD (Singular Value Decomposition) and FT (Fourier Transform)-based methods are popular and widely used for estimating PW-MRI parameters. However, from the published literature it appears that SVD is more widely accepted than other method. In a previous article, an FT-based MMSE technique was proposed and simulation experiments were performed to compare it with the well established oSVD method. In this study, the FT-based MMSE method has been used to estimate relative CBF in 8 patients with white matter lesions (leukoaraiosis) and results are compared with the widely used circular SVD (oSVD) method.

Materials and Methods—8 patients with leukoaraiosis were imaged on a 1.5T Siemens whole body scanner. After acquiring the localizer and structural scans consisting of FLAIR, T1 and T2w images, perfusion study was implemented as part of the MRI protocol. For each patient and method two values were calculated: 1) relative CBF for NWM, obtained by dividing the average ROI CBF value in NWM with average CBF in GM and 2) relative ROI CBF for WML, obtained by dividing the average flow value in WML with average flow in GM.

Results and Discussion—A significant ($p < 0.05$) decrease in estimated CBF was observed in the WML in all the patients using MMSE method, while for the oSVD method, the decrease was observed in all but one patient. Initial results suggest that MMSE method is comparable to oSVD method for estimating CBF in NMW while it may be better than oSVD for estimating flow in low flow lesions. Studies in a larger patient population may be required to further validate this finding.

Keywords

MRI; perfusion; cerebral blood flow; CBF; leukoaraiosis; SVD; FT-MMSE

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Introduction

The bolus-tracking (BT) technique is the most popular PW DSC-MRI method used for estimating CBF, CBV and MTT. The BT technique uses a convolution model that establishes the input-output relationship between blood flow and the vascular tracer concentration. SVD (Singular Value Decomposition) and FT (Fourier Transform)-based deconvolution methods are popular and widely used for estimating PW-MRI parameters. However, from the published literature it appears that SVD is more widely accepted than other method. In a previous article, an FT-based minimum mean-squared error (MMSE) technique was proposed and simulation experiments were performed to compare it with the well-established circular SVD (oSVD) method. In this study, the FT-based MMSE method has been used to estimate relative CBF (rCBF) in 13 patients with white matter lesions (leukoaraiosis) and results are compared with the widely used oSVD method.

Materials and Methods

13 patients with leukoaraiosis were imaged on a 1.5T Siemens whole body scanner. After acquiring the localizer and structural scans consisting of FLAIR, T1 and T2w images, perfusion study was implemented as part of the MRI protocol. For each patient and method two values were calculated: 1) relative CBF for normal white matter (NWM) ROI, obtained by dividing the average CBF value in NWM ROI with average CBF in gray matter (GM) ROI and 2) relative CBF for white matter lesion (WML) ROI, obtained by dividing the average CBF value in WML ROI with average CBF in GM ROI. Results for the two deconvolution methods were computed.

Results and Discussion

A significant ($p < 0.05$) decrease in estimated rCBF was observed in the WML in all the patients using MMSE method, while for the oSVD method, the decrease was observed in all but one patient. Initial results suggest that MMSE method is comparable to oSVD method for estimating rCBF in NWM while it may be better than oSVD for estimating rCBF in lesions of low flow. Studies in larger patient population may be required to further validate the findings of this work.

Introduction

The estimation of physiological parameters such as blood flow provides useful functional information about tissue health. In the last decade, application of perfusion weighted (PW) MRI technique based on dynamic susceptibility contrast (DSC) MRI has gained popularity and is now widely used for investigating neurological disorders such as stroke.

In order to extract meaningful information from perfusion-weighted data, i.e. cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit-time (MTT), the acquired MRI data has to be post-processed. There are two techniques that are widely used for estimating PW-MRI parameters - the Singular Value Decomposition (SVD)-based and Fourier Transform (FT)-based methods[1]. However, from the published literature and available software programs, it appears that SVD-based deconvolution method is more widely used than other deconvolution methods [1,5,8,9]. In a previous publication [2], we proposed a modified FT-based method that involves derivation of an optimally-shaped filter (defined as a function of frequency) estimated using MMSE technique in the Fourier domain. The proposed technique was compared with the well-established oSVD technique using simulation experiments. In addition, the effect of arterial input function (AIF) distortion, SNR and bolus delay on estimated CBF values using the oSVD and the proposed method was investigated using simulation experiments.

A natural next step would be to demonstrate the application of the proposed technique to the real-world MRI data. Hence, in this work we have applied the FT-based MMSE method to estimate relative CBF (rCBF) in elderly patients with white matter (WM) lesions. The patients were recruited as part of a larger NIH funded study that involves characterization of WM lesions using MRI and MRS methods in an elderly population. The WM lesions in these patients have high signal on T2-weighted images and demonstrate periventricular lucency on CT images. As a result, the radiological finding has been termed “leukoaraiosis”. Studies performed in the post mortem brain show that severe leukoaraiosis is almost always associated with multiple lacunar infarcts, and the small perforating arteries seem abnormal with hyalinization and thickening of the vessel wall. The observed pathology is most common in areas with low perfusion pressure, hence, it is common in areas that are vulnerable to episodes of hypoperfusion. As a result, accurate estimation of CBF in these regions is of interest to clinicians and research investigators and a quantitative assessment of CBF is of value in planning management strategies in these patients. Additionally, CBF may potentially be of value as a neuroimaging biomarker for assessment of disease progress and evaluation of novel drug treatment methods.

In this study, cerebral blood flow studies (CBF) were performed using MRI in patients with demonstrated white matter lesions based on the hypothesis that chronic hypoperfusion-induced hypoxia may be one of the underlying mechanisms of the disease process. CBF studies were done using the well-established bolus-tracking technique based on the DSC method. Thus, the main aim of the study was to compare relative CBF in the WM in elderly patients with white matter lesions (WML), defined as ratio of CBF(WML) to CBF(NGM), and CBF(NWM) to CBF(NGM) using the oSVD and FT-based MMSE method, where NGM denotes normal gray matter, and NWM denotes normal white matter.

Materials and Methods

In this study, 13 patients (age range 52-86 years, mean 72.7 years, 8 males and 5 females) were recruited for the perfusion MRI study. The study protocol was reviewed and approved by the institutional ethics review board and all participants gave written informed consent prior to the study. These patients were examined by board-certified neurologists and identified as potential candidates for this study. Preceding the patient study, MRI parameters such as TE, TR, FOV, MTX size, contrast agent dose were heuristically optimized on healthy controls in order to obtain the most T2* effect, hence, the most contrast signal. For patients, prior structural MRI examination of the visible lesions in the white matter (WM) was also used to make a decision to further have the perfusion study with the contrast agent, Gd-DTPA. There is growing concern regarding the renal adverse effects of Gd-DTPA, especially for the elderly population, who might be at higher risk [7]. Since the study involved elderly subjects, only patients who have WMLs that were bigger than certain amount were used in the perfusion study.

The MRI study was performed in a whole-body Siemens Sonata 1.5T MRI scanner (Siemens, Erlangen, Germany) retrofitted with 40mT/m gradients. A standard head coil with standard restraints was used to fix the subject's head. Before the subjects were positioned in the magnet, a 16 gauge cannula was placed into the antecubital vein. The cannula was then connected to a power injector (Spectris Solaris®, MEDRAD, Warrendale, PA, USA) to facilitate the delivery of Gd-DTPA to the patient at a specific rate and dosage.

Initial localizer images were acquired using the following parameters: 2D FLASH (Fast Low Angle SHot), TR/TE 20/5 ms, matrix 256 × 128, FOV 300 mm × 300 mm, slice thickness 10mm, 1 slice per plane. After the localizer images were acquired, T1-weighted, T2-weighted and FLAIR images were acquired using the following parameters: T1-weighted 3D MP RAGE (Magnetization Prepared with Rapid Acquisition Gradient recalled Echo), sagittal plane, TR/

TE 12/4.76 ms, FOV 220 mm $\times$ 220 mm, slice thickness 1.0 mm, slice gap 1.0 mm, number of slices 128, flip angle 20°, matrix 256 $\times$ 256, number of averages 1, pixel bandwidth 110 Hz; T2-weighted 2D RARE (Rapid Acquisition with Relaxation Enhancement), axial plane, TR/TE 9040/64 ms, FOV 220 mm $\times$ 220 mm, slice thickness 1.5 mm, echo train length 5, slice gap 1.0 mm, number of slices 120, matrix 192 $\times$ 192, number of averages 1, pixel bandwidth 150 Hz; 2D FLAIR (Fluid Attenuated with Inversion Recovery), axial plane, TR/TE/IR 6000/358/2100 ms, FOV 220 mm $\times$ 220 mm, slice thickness 1.5 mm, echo train length 107, number of slices 120, matrix 192 $\times$ 192, number of averages 2, pixel bandwidth 745 Hz;

The perfusion protocol was implemented by prescribing 6 axial slices off the sagittal localizer with the lowermost slice aligned with the superior border of corpus callosum. Since a spectroscopy protocol was also implemented as part of the larger MR protocol, the aim was to slice-match the perfusion slice prescriptions to the spectroscopy protocol. T2*-weighted 2D single-shot GE-EPI (Gradient Echo-Echo Planar Imaging), in axial plane, with TR/TE 1600/78 ms, FOV 220 mm $\times$ 220 mm, matrix 128 $\times$ 128, number of slices 6, slice thickness/gap of 5.0 mm/5.0mm, number of averages 1, and 1345 Hz pixel bandwidth was used. 0.025 mM/kg of Gd-DTPA was injected into the patients at the rate of 4 ml/s using the MR-compatible power injector, followed by 20 ml of saline flush through the venous line. The contrast-agent was injected about 10s after the beginning of data acquisition in order to obtain a pre-bolus baseline data set. The total duration of the acquisition was 85s. Images acquired before the contrast-agent injection were used as reference images.

Data were reviewed on the scanner prior to transferring it to an offline workstation for further processing. A MATLAB (7.2.0 R2006a, Mathworks, Natick, MA)-based perfusion graphical user interface (GUI) software (Center for Functionally Integrative Neuroscience, Aarhus University Hospital, Denmark)[8] was used to calculate CBF maps; the original software used oSVD deconvolution method and it was modified to apply the recently developed FT-based MMSE method. After the CBF maps were calculated, AIF was automatically estimated for each slice by the software, and an optimal AIF was selected for each patient by the operator by examining the arrival, sharpness, and proximity of the estimated AIF curves to the anterior cerebral artery. Same optimal AIF was used by both methods. Data processing was performed such that the all the pre-processing steps for calculating CBF maps were similar and differed only in the application of the deconvolution method. Representative ROIs were drawn manually by a trained neurologist on the perfusion-weighted raw EPI images in the regions of normal white matter (NWM), white matter lesion (WML) and (normal) gray matter (GM) under the guidance of the FLAIR and T2-weighted structural images, by using ImageJ software (ImageJ, NIH). For slices that lesions can be visually seen on FLAIR and/or T2-weighted images, approximately slice-matched EPI image was selected, and one ROI for each of WML, NWM and GM regions was drawn and saved. Then, the CBF map for the same slice was loaded and the ROIs were overlaid on the CBF map. Mean value and standard deviation of the CBF in these three ROIs as well as area of the ROIs were calculated and then read into a spreadsheet for further analysis. For a particular slice, the following two values were calculated from the three ROI mean values: 1) relative CBF (rCBF) for NWM, obtained by dividing the mean CBF value in NWM ROI with mean CBF value in GM ROI and 2) rCBF for WML, obtained by dividing the mean CBF value in WML ROI with mean CBF value in the same GM ROI that was used for calculation of 1). This was repeated for all slices that had lesions (usually between 2-4 slices), and, from these multi-slice results, area-weighted average rCBF values of NWM and WML were calculated for the patient. This procedure was repeated for all the patients. Statistical analysis was performed in Excel (Microsoft) (using the add-in statistics toolbox) using students' paired t-test. Paired test allowed only the effect of two methods to be compared, i.e., it disallowed any external inter-subject variations of rCBF to effect the comparison (e.g. changes in patient physiology, metabolism, weight, age, gender, nutrition, etc.). DSC PWI

methods are still not quantitative due to unquantified effect of these factors on CBF, and this makes it relevant to define and use relative CBF measures, such as done in this work.

Results

Figure 1 shows a plot for temporal profile of the bolus passage in pixels representing a region of the artery, NWM and WML in a single slice of one of the patients. The Y-axis of the plot is the percentage of the change in signal due to T2* effect from the first passage of the bolus while the X-axis represents the number of phases or data points acquired during application of the perfusion protocol. As expected, the highest change in signal intensity due to first passage of bolus was observed in the pixel that contains an artery (in this case the anterior cerebral artery). Additionally, it was observed that the percentage change in signal, in pixels representing the NWM is about twice that of the pixels representing the WML.

Figure 2 shows FLAIR image of single slice from one of the 13 patients recruited in this study with the corresponding CBF color maps obtained using oSVD-based and FT-based MMSE methods. The lesions seen as bright regions in the WM are seen as conspicuous regions with reduced flow and they are heterogeneously distributed in the WM. ROI analysis was performed using these color maps and rCBF values for NWM and WML were calculated and used for further analysis. There was a significant ($p < 0.05$, paired t-test) decrease in CBF in the WML compared to the NWM in all the patients as shown by oSVD ($p = 0.00096$) and FT-based MMSE method ($p = 0.00098$). With the oSVD method, the relative CBF value was higher in WML compared to the NWM in one patient. This was not observed with the FT-based MMSE method. The two methods did not produce significantly different results from each other neither in NWM ($p = 0.277$, paired) nor in WML ($p = 0.096$, paired). However the almost three-fold difference between NWM and WML significance suggests that the two methods produce less similar results in WMLs when compared to NWM results, suggesting more uncertainty in WML results.

Figure 3 shows box-and-whiskers plot for CBF estimates for NMW and WML, obtained using the oSVD deconvolution and FT-based MMSE deconvolution methods. Both methods showed a significant decrease in CBF in WML. The inter-quartile range (IQR) for the relative CBF was 0.179 and 0.214 for NWM; 0.164 and 0.128 for WML by using the oSVD and FT-based deconvolution methods, respectively. The full range of rCBF values are 0.400, 0.440, 0.353, 0.397, respectively. Data-spread for rCBF values for NMW was similar for both methods, with FT-based method having slightly greater IQR and full data range. However, the data-spread for rCBF values in WML was different; FT-based results had 40% less IQR than that of oSVD, although the data range was 13% greater. This suggests outlier-like behavior for FT-based results in WML. The median rCBF values estimated were similar for both methods; they were 0.426, 0.417 in NWM, and 0.321, 0.324 in WML, for oSVD-based and FT-based methods, respectively. The average relative CBF values for NWM, WML were 0.413 ± 0.122 , 0.305 ± 0.106 for oSVD technique and 0.423 ± 0.141 , 0.337 ± 0.117 for FT-based technique (mean $\pm$ standard deviation (SD)), respectively. Mean and SD results present similarity between the two methods, with FT-based method results being slightly higher (+2.5% in NWM and +10% in WML) and more spreaded (+16% in NWM and +10% in WML). For the oSVD method, the median values are slightly greater than the mean, suggesting that the data distribution is slightly skewed towards the upper end, whereas it is the exact opposite case for the FT-based MMSE method.

Figure 4 is a scatter graph of rCBF values obtained using scatter plot of the FT-based rCBF results versus the oSVD-based rCBF results. It shows a linear regression fit with forced intercept at origin for the NWM (Figure 4A) and WML (Figure 4B) data values. The goodness-of-fit measure, i.e. the r^2 values, for the linear fit to the NWM and WML data are 0.853 and

0.446, respectively. High r^2 for NWM data with respect to low/moderate r^2 for WML data suggests that algorithms produce similar results for NWM, whereas they differ for WML. This is consistent with the suggestion that WMLs are regions with higher uncertainty in terms of rCBF estimation with respect to NWM regions. This suggests that WMLs have low SNR. Low amount of flow is the main reason for low SNR in WMLs, which makes it harder for algorithms to estimate the CBF reliably.

Discussion

The bolus-tracking method based on DSC-MRI is the most widely used MRI technique for measuring local blood flow. However, the raw data acquired using this technique has to be post-processed using deconvolution methods before any meaningful information can be obtained from these images. The two most commonly used deconvolution methods are SVD-based and FT-based techniques. In a previous publication, we had discussed the advantages and disadvantages of both of these techniques. In the same publication, an FT-based MMSE method was proposed to derive and characterize the shaped filter function by estimating the SNR rather than derive it empirically by assuming an arbitrary filter function. The filter function would then be used to obtain a residue function from which flow can be estimated while in the frequency domain. The potential advantages of such a filter function would be the ability to optimally filter high frequency components, reduce noise component in the signal and the reliability of estimated CBF values. A simulation study was performed in which the proposed deconvolution method was compared with the existing oSVD method. The results of the simulation experiments suggested that the proposed FT-based MMSE technique was comparable to oSVD method in absence of AIF distortions and was insensitive to AIF delays. However, the true test of the proposed technique would be its application to real world MRI blood flow data.

In this study, the FT-based MMSE method has been used to estimate relative CBF values in NWM and WML in patients with leukoaraiosis and the results have been compared with the more popular oSVD method. The aim of the study was to demonstrate the application of the proposed technique for estimating relative blood flow in a clinical setup and compare its performance with the more popular oSVD method. Patients with leukoaraiosis provide an interesting population to study, since global chronic cerebral hypoperfusion has been postulated to be one of the mechanisms underlying the disease process[3]. It has been hypothesized that hypoxia-induced chronic cerebral hypoperfusion is responsible for the damage to the white matter, which are visible as bright regions on the T2 weighted images (also known as Leukoaraiosis)[4].

The deconvolution methods were successful in demonstrating that relative CBF values in WML were significantly lower than NWM, which is in agreement with the pathophysiology of leukoaraiosis. There was slight difference between the oSVD and the FT-based MMSE methods in terms of the estimated relative CBF values in NWM and WML. It was observed during data analysis that there was a systematic inter-subject variation in relative CBF estimates in NWM and WML respectively. It can be postulated that the source of variation might be differences between subjects such as physiology, metabolism, age, gender, nutrition, etc. as well as operator-induced errors due to limited ability to consistently and accurately segment NWM, WML and GM manually, and/or the effects of partial volume effects due to thick slices and large voxel size. Co-registration of CBF maps with anatomical scans using rigid body transformation and the use of sophisticated semi-automated segmentation techniques may have helped alleviate some of the inter-subject variation in rCBF values. Though the improper selection of AIF values and effect of bolus dispersion cannot be ruled in this case, the AIF was automatically selected by the software for each patient based on common criteria, was assumed

to be optimal and thus, may not have had a significant effect on the inter-subject variation of estimated CBF values.

The FT-based MMSE method was found to have less IQR in the WML when compared to the oSVD method suggesting a reduced data-spread with the former as compared to the latter. FT-based MMSE method is inherently adaptive to the noise level [2] and is more regulatory in low-flow, low-contrast, low-SNR regions so that it potentially does not overestimate the low flow values. The IQR for the NWM were comparable between the techniques. In one patient, the relative CBF value in the NWM was found to be (~15%) lower than the WML with the oSVD method, whereas it was not observed with the FT-based MMSE method. This might be due to operator error in manual delineation of ROIs, or, due to a limitation of oSVD method, or both. However, same exact ROIs were used for both methods, and the result might as well be due to overestimation of oSVD method. oSVD method uses a fixed oscillation index based on certain SNR assumption, to reject singular values that will be not be used for estimating CBF [5]. On the other hand, the FT-based MMSE method involves estimation of an optimal shaped filter, $\phi^*(f)$, derived using the minimum mean-squared error method (please see previous publication for derivation of the shaped filter)[2]. The deconvolution methods are essentially mathematical methods used for solving for impulse-residue function. SVD and FT methods represent two broad classes of methods that are available to us for solving deconvolution problems. The FT-based MMSE method used in this study for estimation of relative CBF values can be thought of as a variant of a Wiener filter[6]. However, the difference lies in the fact that, in the proposed method, SNR level is estimated for every pixel adaptively based on the model formulated in [2], the optimal shaped filter function is derived based on that estimation pixel-wise, and noise is filtered adaptively, pixel-wise. In some ways, the FT-based MMSE method can be called an adaptive Wiener filter, since it uses pixel-wise noise information to obtain a uniquely shaped filter to selectively reduce the high frequency part of the data that is assumed to be dominated by noise. The filter has been optimized to minimize the sum of the squared deviations between the estimated deconvolved and the 'true' curves. The SVD method on the other hand, uses a thresholding method based on some *a priori* knowledge based on results from optimal Monte-Carlo simulations under assumption of certain SNR, to filter the noise dominant high frequency components. This may result in over or underestimation of CBF, especially, if the SNR assumption is violated in cases of low flow. An adaptive SVD method that takes into account the experimental noise in the data and modifies the oscillation index by optimally estimating it based on the signal to noise ratio, could be implemented, albeit at cost of high computation time. In comparison, the proposed method is robust and computationally efficient, thereby making it more attractive for routine clinical use.

The scatter graphs in Figure 4 demonstrate an interesting observation i.e. the relatively high correlation between CBF values estimated using oSVD and FT-based MMSE techniques in NWM compared to the flow in WML. This finding suggests that there is good agreement between deconvolution methods within a certain range of flow values (more in the high-flow range), but the agreement is no longer good for the low-flow case, suggesting the uncertainty and high noise level conditions for those regions. Studies in larger patient population that offers a wider range of flow conditions and phantom studies would be required to measure individual algorithms' performances in low-flow conditions reliably and conclusively.

In this study, the dosage of Gd-DTPA was 1/4th of the dose normally used in typical perfusion studies (~0.1 mM/kg). The main reason for use of this dose was due to the fact that this dose was optimal for another contrast enhanced study that was part of the study protocol and is beyond the discussion of this study. On a positive note, the use of quarter dose Gd-DTPA produced a significant T2* change in MR signal in the anterior cerebral artery as evident from Figure 1, partly supported by choice of optimal MR parameters sensitive to T2* effects,

allowing derivation of an optimal AIF. Additionally, the use of low dose Gd-DTPA in this study should be seen as an advantage, since this study involved elderly subjects and there is growing concern regarding the renal adverse effects of Gd-DTPA[7]. The elderly population may be at higher risk, particularly those with compromised renal function.

Conclusion

The bolus-tracking technique is the most popular DSC-MRI method used for estimating CBF. In this study, an FT-based MMSE technique that was proposed previously has been applied for estimating relative CBF in 13 patients with leukoaraiosis and the results have been compared with the well-established oSVD technique. Initial results suggest that the FT-based MMSE method is comparable to oSVD method for estimating CBF in NMW while it may be better than oSVD for estimating CBF in low flow lesions. Future work involves extending the analysis to a larger patient population in order to further validate the technique.

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Figure 1.

shows a plot of change in MR signal intensity due to the first pass bolus of Gd-DTPA in one of the patients. The MRI parameters were optimized to maximize the sensitivity of the MR signal to T2* effects due to passage of Gd-DTPA bolus. An optimal AIF was derived for each patient from pixels that reflect the sharpest bolus passage (typically from arteries).

Figure 2. shows a (a) slice-matched FLAIR image and the corresponding CBF color maps for (b) oSVD and (c) FT-based MMSE technique. Note the white matter lesions seen on the FLAIR image (black arrow) are also visible on the CBF color maps as regions with reduced blood flow (white arrow points to one of the lesions). Qualitative visual analysis of the FLAIR image and the corresponding color maps shows that the regions with reduced blood flow matched well with the lesions seen on FLAIR image.

Figure 3. shows a series of box-and-whiskers plots with Y-error bars and the means for relative CBF estimates in normal white matter (NWM) and white matter lesions (WML) in 13 patients obtained using oSVD and FT-based MMSE methods. Y-error bars represent the range of data. Please see text for details.

Figure 4. shows a scatter plot with linear regression line fit to relative CBF values obtained using oSVD and FT-based MMSE methods from 13 patients for (A) NWM and (B) WML .