MAJOR PAPER

Effect of Regional Tracer Delay on CBF in Healthy Subjects Measured with Dynamic Susceptibility Contrast-Enhanced MRI: Comparison with ^{15}O -PET

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(Receive February 9, 2005; Accepted March 30, 2005)

Purpose: Deconvolution based on truncated singular value decomposition (SVD deconvolution) is a promising method for measuring cerebral blood flow (CBF) with dynamic susceptibility contrast-enhanced magnetic resonance imaging (DSC-MRI), but it has proved extremely sensitive to tracer delay. The purpose of this study was to investigate the effect of regional tracer delay on CBF determined by SVD deconvolution (SVD-CBF). SVD-CBFs with and without correction for the delay were compared with CBF measured by positron emission tomography (PET-CBF), which is regarded as the gold standard for quantification of CBF.

Methods: Perfusion MRI and PET were performed on seven healthy men. In the PET study, the CBF image was obtained with bolus injection of H_2^{15}O and continuous arterial sampling. In the DSC-MRI study with bolus injection of Gd-based contrast agent, dynamic perfusion data were obtained with a 1.5T scanner at 1-s intervals by means of gradient-echo echo-planar imaging. CBF was determined by the SVD deconvolution method with and without correction for the tracer delay. Region-of-interest measurements were obtained in the gray matter (cerebral cortex in the middle cerebral artery territory) and white matter (centrum semiovale).

Results: Tracer delay was significantly longer in white matter than in gray matter (1.45 ± 0.61 s vs. 0.59 ± 0.35 s, $P < 0.01$). Correction for the delay increased SVD-CBF in the white matter and consequently reduced the gray-to-white SVD-CBF ratio. The uncorrected gray-to-white SVD-CBF ratio was significantly larger than that of PET-CBF (3.33 ± 0.66 vs. 2.54 ± 0.49 , $P < 0.01$). However, the gray-to-white delay-corrected SVD-CBF ratio did not differ significantly from that of PET-CBF (2.83 ± 0.31 vs. 2.54 ± 0.49 , $P = 0.10$).

Conclusion: The tracer delay in DSC-MRI causes errors in CBF estimates, even in healthy persons, and therefore should be corrected for when delay-sensitive deconvolution, such as SVD deconvolution, is used.

Keywords: *cerebral blood flow, dynamic susceptibility contrast-enhanced magnetic resonance imaging, tracer delay, singular value decomposition, positron emission tomography*

Introduction

Cerebral blood flow (CBF), cerebral blood

volume (CBV), and vascular mean transit time (MTT) can be determined with dynamic susceptibility contrast-enhanced magnetic resonance imaging (DSC-MRI). When the arterial input function (AIF) for each brain tissue is accurately determined, deconvolution with the AIF provides

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quantitative CBF; this enables MTT to be calculated from CBV/CBF.^{1,2} Deconvolution by means of truncated singular value decomposition (SVD deconvolution) is a promising method for quantitative MR perfusion study.^{2,3} Relatively good correlation between CBF determined by SVD deconvolution (SVD-CBF) and CBF measured by positron emission tomography (PET) or single photon emission tomography has been reported in animals,⁴ healthy humans,^{5,6} and stroke patients.⁷⁻⁹

SVD deconvolution, however, is extremely sensitive to the difference in tracer arrival time between brain tissue and AIF.^{2,10} Regional tracer delay, which frequently occurs in patients with ischemic cerebrovascular disease, introduces errors into CBF and MTT estimates; consequently, delineation of the tissue with abnormal perfusion is affected.¹¹⁻¹⁴ Regional differences in tracer arrival time have also been reported in normal brains.^{5,15-17} Although regional tracer delay in the normal brain is expected to be small, at less than a few seconds, simulation studies have shown that a small delay can cause a large error in SVD-CBF for tissue with a relatively short MTT.^{2,10,14} Moreover, multi-slice imaging can cause apparent regional delay due to the difference in acquisition time for each slice.¹⁸ These effects result in SVD-CBF errors even in the normal brain without an ischemic lesion. Therefore, when delay-sensitive deconvolution is used for CBF quantification, the effect of regional tracer delay should be corrected for, regardless of whether the subject is a healthy individual or a patient with cerebrovascular disease.

To investigate the effect of regional tracer delay on SVD-CBF in the normal brain, we performed a perfusion study in healthy humans and applied the delay correction method previously reported.¹⁴ SVD-CBF was compared with CBF measured with PET (PET-CBF) in terms of the gray matter to white matter CBF ratio. We hypothesized that SVD-CBF with correction for the delay is more reliable than SVD-CBF without correction and closer to PET-CBF, which is regarded as the gold standard.

Materials and Methods

Subjects

Perfusion MRI and PET were performed on seven male volunteers aged 20 or 21 years. The volunteers were recruited, gave written informed consent, and were judged healthy based on their medical histories, blood screening tests, anatomical MR imaging of the brain, and MR angiography of the brain.

MRI scanning

MRI was performed with a 1.5T whole-body scanner (Magnetom Vision, Siemens Medical Systems). Axial fast spin-echo T₂-weighted images (TR, 3600 ms; TE, 96 ms; number of excitations, 1; field-of-view, 230 mm; slice thickness, 5 mm; 19 slices) were obtained parallel to the anterior commissure-posterior commissure (AC-PC) line. The perfusion data were obtained by single-shot gradient-echo echo-planar imaging (EPI) (TR, 1000 ms; TE, 66 ms; flip angle, 90°; matrix size, 128 × 128; field of view, 230 mm; slice thickness, 5 mm). Twenty seconds after the start of scanning, 10 ml of gadodiamide (Omniscan) was injected into the antecubital vein over a period of three seconds followed by injection of 10 ml of saline. We obtained 120 brain images with a one-second repetition time. Each brain image contained five slices that were identical in position to the five slices of the T₂-weighed image: one slice covered the cerebellum (1st slice) and the other four slices were of the cerebrum at 0 mm (2nd), 12 mm (3rd), 24 mm (4th), and 36 mm (5th), above and parallel to the AC-PC line. The slice-to-slice scan interval was 200 ms.

MRI Data Analysis

CBF determination

The raw image data were processed with a 3 × 3 uniform smoothing kernel. From the dynamic data of 120 frames at one-second intervals, 60 sequential frames were extracted, which provided an adequate number of baseline frames before the agent arrived. The data were further processed to calculate the CBF. The origin of time axis (0-s) was assigned to the first of the 60 frames for each slice. The MR signal intensity was converted to tracer concentration by assuming a linear relation between changes in the transverse relaxation rate and the tracer concentrations.

Determination of CBF is based on indicator-dilution theory.¹⁹ The tracer concentration in each pixel as a function of time after the bolus injection is calculated as follows:

$$C(t) \propto \text{CBF } C_a(t) \otimes R(t), \quad (1)$$

where $C_a(t)$ is the AIF and $R(t)$ is a residue function that represents a residual probability as a function of the time after tracer arrival. After this equation was solved by SVD deconvolution, SVD-CBF was determined as the maximum value of the residue function.^{2,3} The cutoff level in SVD deconvolution was fixed at 15% of the maximum singular value.²⁰ A previously reported semiautomated method was used to measure the AIF in the brain region that covered the insular segment in the middle cerebral

Fig. 1. Typical AIF ($C_a(t)$) and tissue curves ($C(t)$) in the DSC-MRI experiment. Each tissue curve was measured in one pixel including gray matter or white matter tissue. Least-squares fitting reproduced upslopes of the tissue curve well.

artery (MCA) territory (2nd slice).¹⁴ Relative CBF was calculated by multiplying a normalization factor. This factor was determined for each subject as white-matter CBF being 1.0 in a subsequent region of interest (ROI) analysis. Normalization was performed before the delay correction described below.

Delay correction

Delay-corrected SVD-CBF was determined by SVD deconvolution after time-shifting of the tissue curve.¹⁴ The values for regional tracer delay were determined by means of pixel-by-pixel least-squares estimation with a fitting function as follows:

$$C(t) = a C_a(t - \text{DELAY}) \otimes \exp(-b t), \quad (2)$$

where a , b , and DELAY are fitting parameters. In this method, the values of delay (DELAY), which were used for the time-shifting, are not restricted to the sampling interval multiplied by the integer number ($n\Delta t$); for the decimal delay value, the calculation of the sum of squared residuals for the fitting and the time-shifting operation can be performed by linearly interpolating the sampling points in the dynamic data. Only the dynamic data before the concentration peak were used for the fitting because the tail portion would reflect the vasculature rather than the tracer arrival time (Fig. 1). Note that the regional delay determined by the fitting is apparent regional delay including the effect of the difference in acquisition time for each slice (Fig. 2); the origin of time axis (0-s) for each brain tissue (from the 1st to 5th slice) is not synchronous with that for AIF (2nd slice).¹⁸ To obtain the physiologic delay, which is the regional

Fig. 2. This illustrates that the difference in acquisition timing for each slice causes apparent regional delay. In this study, dynamic data for five slices with one-second intervals were obtained (a). The acquisition interval for adjacent slices was 200 ms. The origin of time axis (0-s) was assigned to the first frame of each slice, and the AIF was measured in the 2nd slice. Therefore, the origin of time axis for each brain tissue is not synchronous with that for AIF, resulting in the apparent regional delay (c), even when physiologic delay is absent (b).

delay of tracer arrival in each brain tissue relative to the AIF, a 200-ms interval for acquisition of the adjacent slices must be included in the calculation.

PET scanning

PET-CBF measurement was done with a Head-tome V scanner (Shimadzu Corp., Kyoto, Japan),²¹ which provides 47 sections with a center-to-center distance of 3.1 mm. The intrinsic spatial resolution was 4.0 mm full width at half maximum (FWHM) in-plane and 4.3 mm FWHM axially. Reconstruction with a Butterworth filter resulted in a final in-plane resolution of approximately 10 mm FWHM.

After transmission scanning for attenuation correction, 180-s dynamic scanning was performed following an intravenous bolus injection of H_2^{15}O (1.5 GBq). The scan sequence consisted of twelve 5-s frames and eight 15-s frames. The arterial input function was determined by continuous measurement of arterial whole blood radioactivity with a beta detector. Delay and dispersion occurring in the beta detector system and the internal-arterial line were corrected with a previously reported method.^{17,22}

PET data analysis

According to the one-tissue compartment model, the radioactivity concentration in a brain region is calculated as:

Fig. 3. MRI and PET images. (a) T₂-weighted image. (b) Segmented gray matter image generated by partitioning the T₂-weighted image. (c) Image of regional tracer delay obtained by DSC-MRI. (d) SVD-CBF image without smoothing. (e) SVD-CBF image. (f) Delay-corrected SVD-CBF image. (g) PET-CBF image. SVD-CBF images were processed by Gaussian smoothing with 10-mm FWHM to match spatial resolution. Circular ROIs were drawn on the images.

$$C(t) = K_1 C_a(t) \otimes \exp(-k_2 t) \quad (3)$$

where $C(t)$ and $C_a(t)$ are the radioactivity concentrations in the brain region and arterial whole blood, respectively. K_1 is the influx rate constant (ml/min/ml) corresponding to CBF, k_2 is the efflux rate constant (1/min), and $\otimes$ denotes the convolution operation. K_1 and k_2 were determined by pixel-by-pixel least-squares estimation. The weights for least-squares estimation were derived from the radioactivity curve for the whole brain.^{23,24}

ROI analysis

The PET-CBF images were registered to the individual anatomical MR images (T₂-weighted images) with SPM.²⁵ The SVD-CBF images were processed with a Gaussian filter with 10-mm FWHM to match the spatial resolution of DSC-MRI with that of PET. With the T₂-weighted images used as anatomical references, circular ROIs 10 mm in diameter were identified bilaterally for cerebral cortices in the MCA territory (12 ROIs on the 2nd to 5th slices in the SVD-CBF image) and

centrum semiovale (6 ROIs on the 5th slice; Fig. 3). Average gray matter (cerebral cortex in the MCA territory) and white matter (centrum semiovale) CBFs were calculated for each subject and subsequently averaged across all subjects. For a comparison of SVD-CBF and PET-CBF, ratios of gray matter CBF to white matter CBF (gray-to-white CBF ratios) were calculated because of the difficulty in determining absolute SVD-CBF due to a partial volume effect for the AIF measurement and some problems in scaling.²⁶ Regional differences in the tracer delay and its effect on SVD-CBF as well as comparison of the gray-to-white SVD-CBF ratio with that of PET-CBF were examined by paired t-test. Significance was accepted at $P < 0.05$.

Care was taken to define the ROIs appropriately for the cerebral cortices, covering only the gray matter and avoiding the white matter and a superficial vascular component that caused an artificially large CBF with gradient-echo EPI acquisition.²⁷⁻²⁹ For this purpose, segmented gray matter images, which were calculated from the T_2 -weighted images with SPM with a partitioning algorithm,²⁵ were also referred to as anatomical references.

Results

The results are summarized in the accompanying table. On examination of the DSC-MRI data, the tracer delay was significantly longer in the white matter (centrum semiovale) than in the gray matter (cerebral cortex in the MCA territory; $P < 0.01$). The difference between the two regions was 0.86 s. In the white matter, delay-corrected SVD-CBF was significantly greater (26%) than uncorrected SVD-CBF ($P < 0.05$). In the gray matter, the delay correction did not significantly change SVD-CBF ($P = 0.21$). As a result, the delay-corrected gray-to-white SVD-CBF ratio was significantly smaller than the uncorrected SVD-CBF ratio ($P < 0.05$). The standard deviation of the gray-to-white SVD-CBF ratio was reduced from 20% to 11% by applying delay correction.

The uncorrected gray-to-white SVD-CBF ratio was significantly larger than that of PET-CBF ($P < 0.01$). However, the delay-corrected SVD-CBF ratio did not differ significantly from the PET-CBF ratio ($P = 0.10$).

Discussion

Regional tracer delay in human brain

We investigated the effect of regional tracer delay on SVD-CBF in healthy volunteers. The tracer delay was shown to occur even in individuals

without cerebrovascular disease. Tracer arrival in the white matter (centrum semiovale) was significantly delayed in comparison to that in the cerebral cortex in the MCA territory. The value of the delay in the white matter, 1.45 s relative to the AIF, is consistent with results of a high temporal-resolution DSC-MRI study showing 1.4-s arrival delay in the white matter (centrum semiovale) relative to the MCA.¹⁶ The occurrence of tracer delay in the centrum semiovale of the normal brain is reasonable because the tissues are located at the periphery of the feeding artery (MCA and/or anterior cerebral artery). Although only young volunteers aged 20 or 21 years were examined in the present study, the effect of physiological aging on tracer delay as a perfusion parameter is an attractive object of study. The study of the transcranial color Doppler sonography demonstrated the decline in mean flow velocity with advancing age.³⁰ The aging effect on blood flow velocity suggests the increase in tracer delay for elderly volunteers.

The delay correction increased the white matter SVD-CBF and consequently reduced the gray-to-white SVD-CBF ratio, highlighting the impact of the delay correction for SVD deconvolution: the delay correction enabled the gray-to-white SVD-CBF ratio to approximate that of PET-CBF. Although the value of regional tracer delay in healthy volunteers was relatively small, SVD-CBF was significantly affected, as can be expected from simulation studies that showed a small delay can cause considerable underestimation of SVD-CBF for a short MTT.^{2,10,14} This arises because the scan interval, typically one to two seconds in DSC-MRI, is too long to represent the rapid kinetics of intravascular tracer when MTT is normal, typically three to five seconds. Earlier, we showed that the effect of regional tracer delay in patients with acute unilateral ischemic stroke is greater in normal tissues or in moderately damaged tissues with a relatively short MTT (a few seconds) than in heavily damaged tissues with a prolonged MTT.¹⁴ Similar trends were observed in other studies of acute ischemic stroke.^{18,31} These findings in normal volunteers and in patients with acute ischemic stroke reflect the importance of delay correction for SVD deconvolution, whether or not brain circulation is retained.

Our previous simulation study showed that the delay correction increases the fluctuation in SVD-CBF.¹⁴ In the present study, however, delay correction reduced the standard deviation of the gray-to-white SVD-CBF ratio (Table). This indicates that the inter-individual variation in SVD-CBF is partly due to the effect of regional tracer delay and that

Table. Summary of results

	Delay (s)	Relative SVD-CBF		PET-CBF (ml/min/ml)
		Uncorrected	Delay-corrected	
White matter	1.45 ± 0.61* (0.85 ± 0.61)†	1.00	1.26 ± 0.20‡	0.222 ± 0.036
Gray matter	0.59 ± 0.35 (0.22 ± 0.35)	3.33 ± 0.66	3.55 ± 0.54	0.553 ± 0.067
Gray-to-white CBF ratio	—	3.33 ± 0.66§	2.83 ± 0.31‡	2.54 ± 0.49

Values are shown as mean ± standard deviation.

Significant difference from tracer delay in gray matter (paired t-test): *P < 0.01, †P < 0.05.

Significant difference from uncorrected value (paired t-test): ‡P < 0.05.

Significant difference from gray-to-white PET-CBF ratio (paired t-test): §P < 0.01.

Values in parentheses represent the apparent tracer delay including the effect of the difference in acquisition time for each slice. This apparent tracer delay was used for the delay correction. Because SVD-CBF was normalized to white matter CBF before the delay correction, the uncorrected SVD-CBF of white matter was 1.0 for all volunteers.

delay correction can improve stability of the gray-to-white SVD-CBF ratio.

Comparison with PET-CBF

PET measurement with H₂¹⁵O is regarded as the gold standard for CBF quantification; it can provide stable CBF with absolute units. Our PET-CBF results are consistent with those of previous studies.^{32–34} To compensate for the large difference in spatial resolution between SVD-CBF and PET-CBF images, we applied Gaussian smoothing with 10-mm FWHM to SVD-CBF images. The smoothing increased SVD-CBF of the white matter by 18% (spillover from the cortex) and decreased SVD-CBF of the cerebral cortex by 6% (dilution). This achieved a 20% reduction in the gray-to-white SVD-CBF ratio, with the result approaching the value of the PET-CBF ratio (data not shown).

After resolution matching by smoothing, SVD-CBF images still differed from PET-CBF images. The difference could be partly attributable to image distortion with the single-shot EPI acquisition. Moreover, an artificially large CBF with DSC-MRI appeared as a result of a superficial vascular component.^{27–29} This is an inherent problem derived from the use of intravascular tracer and enhanced susceptibility of large vessels in gradient-echo EPI.^{26,35,36} The ROI analyses, therefore, do not necessarily provide identical CBF values for PET and DSC-MRI even if image coregistration is performed perfectly with distortion-free images. In other words, the results of the comparison of SVD-CBF and PET-CBF depend on the position of the ROIs. The gray matter SVD-CBF in the present study may be overestimated, although care was taken to avoid contribution from the superficial vascular component in the ROI analysis. The

difference in CBF images between DSC-MRI and PET should be interpreted carefully, considering the difference between tracers (diffusible tracer in PET and intravascular tracer in DSC-MRI) and the sequence-dependent characteristic of MR signals (gradient-echo or spin-echo EPI).^{28,29}

Deconvolution method

In the present study, we incorporated correction for regional tracer delay into SVD deconvolution. Other deconvolution methods providing delay-insensitive CBF estimates are possible. Reformulated versions of SVD deconvolution have been proposed.^{12,18} Smith et al. showed that reformulated SVD deconvolution is equivalent to the Fourier transform method when the SVD cutoff parameters are adjusted, and that errors in SVD-CBF estimates resulting from regional tracer delay should be interpreted as artifacts originating from inadequate assumptions in the standard SVD method.¹⁸ When regional tracer delay is absent, however, underestimation of CBF for a short MTT (a few seconds) is greater with the Fourier transform method than with standard SVD deconvolution.² Therefore, we speculate that SVD deconvolution with the delay correction is, at present, the best method for CBF quantification, although determination of the tracer delay by least-squares fitting should be improved for rapid calculation.

Conclusion

The regional tracer delay in DSC-MRI results in inaccurate estimation of SVD-CBF, although the values of tracer delay in healthy humans are relatively small. The delay correction method described herein provides a gray-to-white SVD-

CBF ratio with less inter-individual variation and closer equivalence to that of PET-CBF. Regional tracer delay is an essential factor in DSC-MRI study and should be corrected for when delay-sensitive deconvolution, such as the SVD deconvolution, is used.

Acknowledgments

The authors thank the technical staff of the Akita Research Institute of Brain and Blood Vessels. This research was supported in part by a Grant-in-Aid for Young Scientists (16790751) provided by the Ministry of Education, Science, Sports and Culture and by the ISMRM2004 *Hiyaku-shou* from the Japanese Society for Magnetic Resonance in Medicine.

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