Magnetic Resonance in Medicine 41:1264–1268 (1999)

# Comparison of Static and Dynamic MRI Techniques for the Measurement of Regional Cerebral Blood Volume

O. Speck,* L. Chang, L. Itti, E. Itti, and T. Ernst

**Two different acquisition and processing strategies to determine the regional cerebral blood volume (rCBV) with magnetic resonance imaging (MRI) are compared. The first method is based on the acquisition of the signal time course during a bolus administration of a contrast agent (dynamic method). The second method evaluates signal changes before and after the contrast agent injection (static method), assuming the contrast agent remains primarily intravascular in the brain after the first pass. Both methods were applied to the same data sets, acquired with either echoplanar imaging (EPI, $n = 18$) or fast low-angle shot (FLASH, $n = 28$) techniques. A voxel-by-voxel correlation between the static and dynamic method yielded a correlation coefficient of 0.76 ± 0.06 for the EPI and 0.71 ± 0.10 for the FLASH measurements. The static method was less sensitive and showed higher standard deviations for rCBV than the dynamic method. With the development of truly intravascular contrast agents, the static perfusion MRI method, which can be performed with higher signal-to-noise ratio and higher spatial resolution, may become an alternative to ultra-fast MRI for measuring rCBV. Magn Reson Med 41:1264–1268, 1999.** © **1999 Wiley-Liss, Inc.**

**Key words: regional cerebral blood volume; fast imaging; perfusion imaging; image processing**

The regional cerebral blood volume (rCBV) is a parameter commonly used in dynamic susceptibility contrast MRI to identify abnormalities in cerebral hemodynamics. For instance, abnormal rCBV has been reported in patients with stroke (1–4), Alzheimer's disease (5,6), human immunodeficiency virus (HIV) dementia (7,8), or cocaine abuse (9). The measurement of the rCBV by means of MR imaging is typically based on the acquisition of the signal time course after the bolus administration of a contrast agent (10,11). rCBV can be determined as the area under the concentration time curve, either by numerical integration or by fitting a model function (gamma-variate function) to the data. Because of the short duration of the bolus passage of the contrast agent (on the order of 10 sec), the signal time course has to be determined with high temporal resolution. Only ultra-fast imaging techniques are able to scan the whole brain with sufficient temporal resolution. The technique most commonly used for this application is echoplanar imaging (EPI). However, EPI has a relatively low spatial resolution and is sensitive to geometric distortions due to inhomogeneities of the magnetic field.

Harbor UCLA Research and Education Institute, Torrance, California.

Grant sponsor: NIH (Scientist Development Award for Clinicians; Grant number: DA 00280; Grant sponsor: State of California Universitywide AIDS Research Program; Grant number: CC97 LA 175; Grant sponsor: French Association for Cancer Research (ARC).

*Correspondence to: Oliver Speck, Department of Neurology Building B-4, 1000 W. Carson Street, Torrance, CA 90509.

Received 3 August 1998; revised 3 February 1999; accepted 11 February 1999.



This study evaluates whether the rCBV can be determined by the static signal changes caused by the contrast agent after its distribution within the vascular system and the inner organs and muscles (12,13). This would allow the use of slower imaging methods with better imaging properties, higher spatial resolution, and higher signal-to-noise ratios.

If the blood-brain barrier (BBB) is intact, the contrast agent should remain intravascular even after the first pass through the brain. Thus, the blood volume in a given voxel is proportional to the concentration of the contrast agent. If the exploited contrast mechanism is the T2* effect of the contrast agent, its concentration $c_{\text{brain}}$ can be calculated as

$$c_{\text{brain}} \sim \ln S_{\text{N}} - \ln S_{\text{C}} \qquad [1]$$

with $S_{\text{N}}$ and $S_{\text{C}}$ being the signal intensities before and after the administration of the contrast agent. By normalizing this to the concentration $c_{\text{blood}}$ in a large vessel, the rCBV can be determined as:

$$\text{rCBV} = \frac{c_{\text{brain}}}{c_{\text{blood}}}. \qquad [2]$$

Most of the published signal time courses show a signal decrease with a reduced baseline after the passage of the bolus (14–18). However, this effect is usually neglected, since only the time points during the first pass are included in the rCBV calculation. In studies that use simulated time courses (to test processing algorithms), the recirculation effects and the resultant lower post-contrast baseline are usually not included (19–21). The goal of this study is to compare the rCBV determined by the dynamic method (the first pass of a contrast agent bolus) and the static method (signal change before and after the contrast agent administration) within the same data sets.

## MATERIALS AND METHODS

All measurements were performed on a 1.5 T whole body scanner (GE SIGNA 5.6, Milwaukee) equipped with a fast gradient set (SR 120). For the perfusion measurement, 39 repetitive scans of 13 slices were acquired with EPI: TE 30 msec, TR 2500 msec, matrix size 64 × 64, field of view (FOV) 20 cm, slice thickness 7 mm. In addition, previous single slice measurements using turbo FLASH imaging (TE 19 msec, TR 38 msec, matrix size 256 × 64 (half-Fourier), FOV 34 × 17 cm, slice thickness 8 mm, 40 scans) were included in the study. After 12 baseline scans, 20 ml of low molecular weight gadolinium-based contrast agent [gadolinium-diethylene triamine pentaacetic acid (Gd-DTPA)] (Prohance; Squibb, Princeton, NJ) were manually injected into the antecubital vein of one arm, with a bolus duration

of approximately 4–8 sec. The scans of 45 normal subjects (17 with EPI, 28 with FLASH) were included in this study. All scans were performed after obtaining written consent from the subjects. The protocol was approved by the Institutional Review Board at Harbor-UCLA Research and Education Institute.

All data sets were processed with both the dynamic and the static method. To evaluate the first pass effect of the contrast agent, a gamma-variate function was fitted directly to the signal-time course of each pixel (20). The static effect was calculated from the 10 first and 10 last time points of each time course using Eq. [1]. Although the contrast agent concentration in the blood might not have completely reached a steady state, the last 10 time points were considered to be the best compromise within the available time window, both to minimize the washout of the contrast agent and to avoid the recirculation region. For both methods, rCBV values were determined for all voxels that exceeded a threshold of 5% of the maximum signal intensity of the entire data set. The results of the two methods were compared by means of a correlation analysis, using the rCBV values of all voxels. Prior to the correlation analysis, a median filter ($3 \times 3$ kernel size) was applied to the rCBV maps. In addition, the rCBV values of manually drawn regions of cortical gray matter, white matter and deep gray matter (including putamen, globus pallidus, caudate, and thalamus) in the brain were determined and compared between the methods. The regions of interest (ROIs) were drawn on the high-resolution MRI scans following the exact anatomy of the brain structures and averaged across all the slices. The high resolution MRIs were coregistered to the rCBV maps using a surface matching registration method developed in our laboratory (22). During this coregistration, geometric distortions of the EPI datasets are corrected using a full affine transformation that also accounts for possible scaling or shearing in phase direction (23). The rCBV values from the ROIs were referenced using three different approaches: 1) relative to the highest rCBV value within a large vessel (typically the sagittal sinus); 2) relative to the mean of the whole brain rCBV (for EPI) or the mean of the whole slice rCBV (for FLASH), which were determined using coregistered perfusion maps and the automatically segmented brain from the high-resolution anatomical scans; and 3) for the EPI scans, relative to the rCBV values of manually drawn ROIs in the cerebellum. All processing was performed using the IDL (Research Systems, Boulder, CO) and the AVS (Application Visualization System, Waltham, MA) software packages, extended with customized modules written in the C-language.

## RESULTS

Figure 1 shows the average signal time course of all voxels in the brain of a normal subject. The considerable drop of the MRI signal during the first pass of the contrast agent bolus is well recognizable, as well as the decreased signal intensity after the bio-distribution of the contrast agent. The signal change during the first bolus passage was approximately 3–4 times as large as the static effect. Figure 2 demonstrates that rCBV maps generated with the dynamic and the static approach appear very similar. The

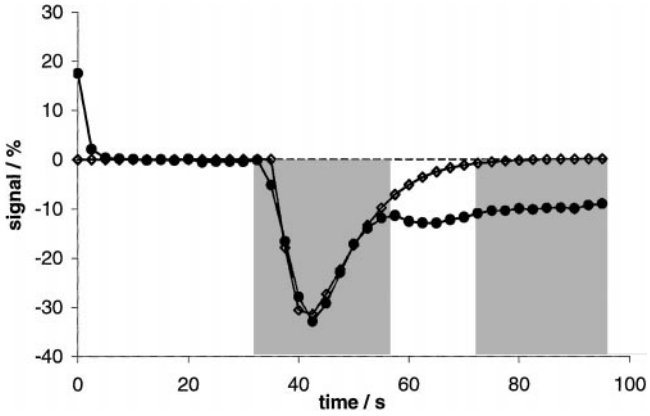


FIG. 1. Average signal time course of all voxels within the brain (circles) and a gamma-variate fit to the data (open diamonds) for an EPI data set from one subject. Compared with the initial baseline, the lower signal intensity after the bolus passage is clearly visible. On average, the maximum signal change during the bolus phase is 3–4 times larger than that during the subsequent pseudo-steady state. The time periods used for the calculation of the dynamic (bolus at ~30–55 sec) and the static (last 10 time points) effects are shaded in gray.

rCBV in the cortical gray and the deep gray matter was higher than in the white matter, and the highest values were reached within the larger vessels.

### Voxel-by-Voxel Correlation

The average number of voxels analyzed per data set was 12,627 ± 1644 with EPI and 7438 ± 1713 with FLASH. The correlation coefficients were r = 0.67 ± 0.18 for the EPI and r = 0.57 ± 0.27 for the FLASH measurements. The correlation coefficients were frequently lower in the inferior slices. In addition, motion during the scans yielded stronger artifacts in the rCBV maps calculated with the static method. When the analysis was restricted to data sets without detectable motion and to pixels within the brain only, the correlation coefficients were improved (r = 0.76±0.06 for EPI, and r = 0.71±0.10 for FLASH). An example of the correlation between the rCBV values in one subject is shown in Fig. 3.

### ROI Analyses

Figure 4 shows the mean rCBV values of cortical gray matter, deep gray matter, and white matter, normalized to the whole brain (EPI) or the whole slice (FLASH). In the gray and deep gray matter regions of the EPI scans, the static method resulted in slightly lower rCBV values. However, two-tailed paired *t*-tests showed that the mean values of the two processing methods were not significantly different for any of the regions tested in the EPI or the FLASH data. (A *P* value of less than 0.05 after Bonferroni correction for multiple testing was considered significant.) The interindividual standard deviations in the relative rCBV values were smallest when the data were normalized to the whole brain or the whole slice, intermediate when normalized to the cortical gray matter or the cerebellum, and largest when normalized to the maximum intensity within the data set. The mean values for the ratios

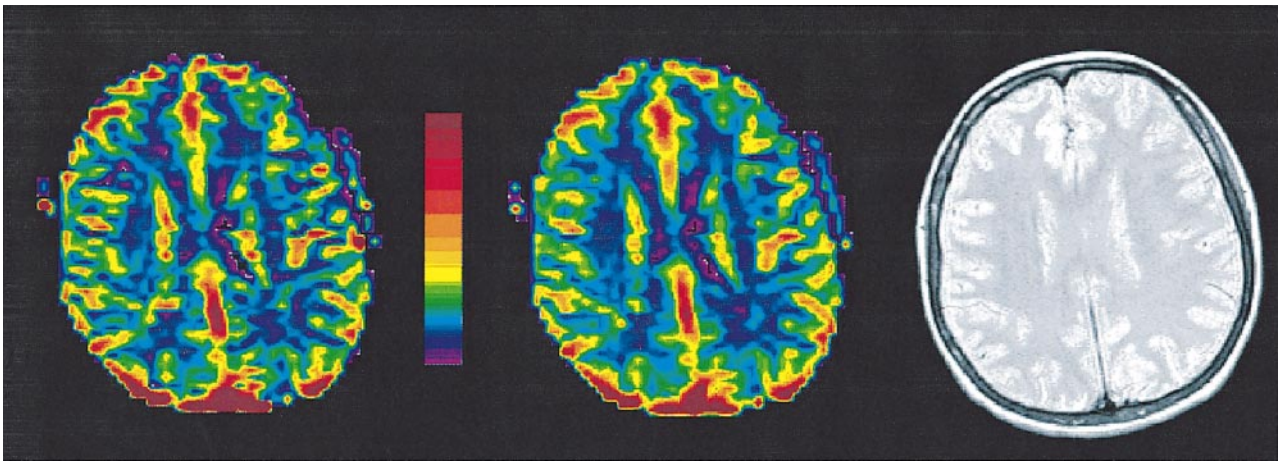

FIG. 2. rCBV maps calculated with the static (left) and the dynamic (middle) methods from one of the EPI scans, as well as a coregistered anatomical scan. The rCBV is higher in the cortical gray and the deep gray matter (caudate) and reaches the highest values in larger vessels. Qualitatively, the two maps are very similar. See Results section for the quantitative analyses.

of all regions are shown in Table 1. The standard errors are generally smaller for the dynamic method.

When the individual rCBV values were referenced to the highest value found within a major vessel (absolute quantitation), we obtained gray matter rCBV values of 0.056 ± 0.02 (dynamic) and 0.014 ± 0.006 (static) from the EPI data and 0.081 (dynamic) and 0.039 (static) from the FLASH measurements.

## DISCUSSION

Our study demonstrates that rCBV can be determined reliably using the MRI signal changes both during and after the first pass of a bolus of contrast agent. The good correlation between the two methods justifies the assumption that the contrast agent in the brain is essentially intravascular even after the first pass. However, an improved correlation was achieved when the perfusion data were restricted to the segmented brain derived from coreg-

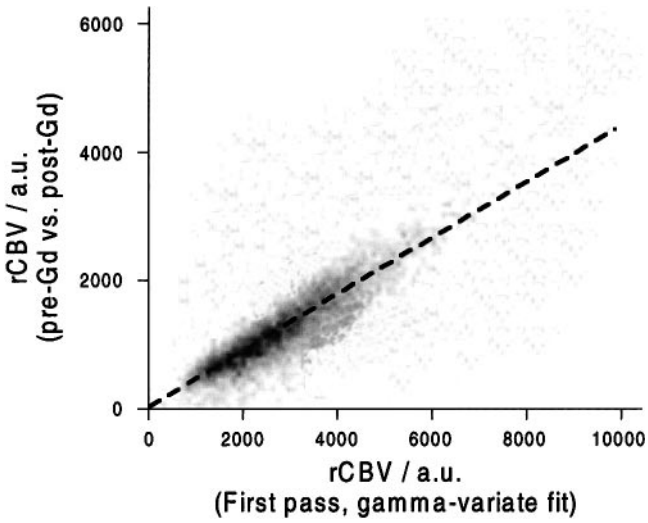


FIG. 3. 2D histogram (density plot) and regression line between the rCBV determined by the dynamic method (gamma-variate fit) and by the static method (pre-Gd versus post-Gd). In this subject, the correlation coefficient was r = 0.82. Although the data seem to suggest an underestimation of the higher values for the dynamic method, a second order regression did not improve the residual error. This may be due to the very high density in the center range of the histogram.

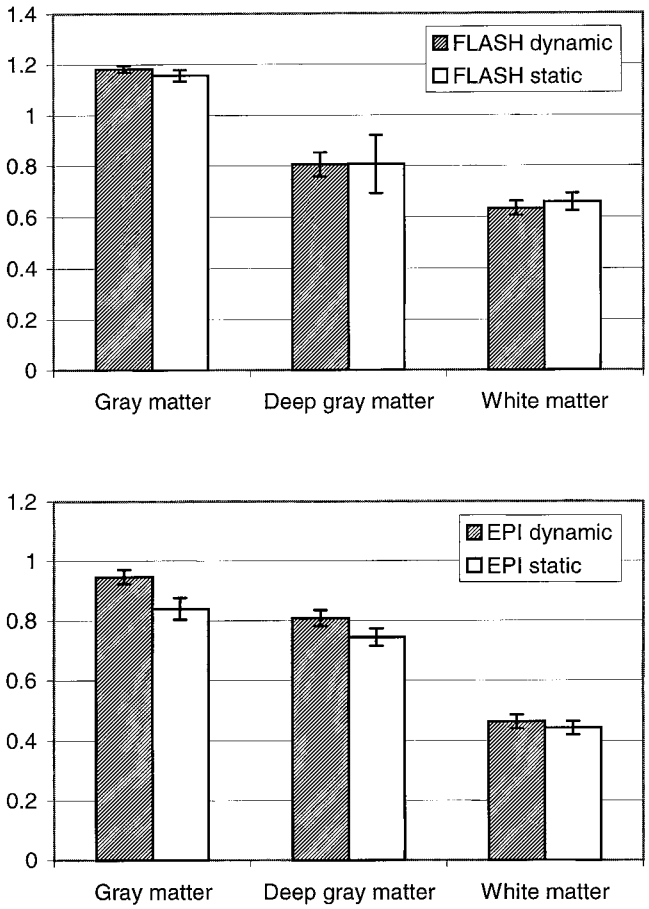


FIG. 4. The rCBV values and standard errors for the different acquisition and processing methods normalized to the mean rCBV values from the whole slice (FLASH) or from the whole brain (EPI). The values for the dynamic and the static methods did not differ significantly in any of the regions tested.

Table 1
Relative rCBV Values of Several Regions Using the Different Acquisition and Processing Schemes (mean ± SE)

| Region | FLASH | | EPI | |
|---|---|---|---|---|
| | Dynamic method | Static method | Dynamic method | Static method |
| White vs. gray | 0.52 ± 0.02 | 0.57 ± 0.03 | 0.50 ± 0.04 | 0.54 ± 0.04 |
| Deep gray vs. gray | 0.70 ± 0.07 | 0.72 ± 0.11 | 0.86 ± 0.04 | 0.90 ± 0.05 |
| Deep gray vs. white | 1.38 ± 0.16 | 1.24 ± 0.19 | 1.77 ± 0.07 | 1.71 ± 0.8 |

istered anatomical MRI. Without this segmentation, the extracranial structures (e.g., facial muscles), which accumulated the contrast agent after the first pass, showed higher rCBV values in the static method compared with the dynamic method since the assumption that the contrast agent remains intravascular is violated in these areas.

The static method was more sensitive to motion artifacts than the dynamic method. Motion typically caused strong signal changes in areas of steep gradients of the signal intensity, such as at the edges of the brain. A motion correction algorithm that is not based on intensity differences but on brain structures may improve the results of the static method. Another possible source of discrepancies between the two methods is the large difference in contrast agent concentration during the time periods analyzed. During the bolus phase of the dynamic method, the assumed linearity between Gd concentration and relaxivity may become invalid, especially in and around large vessels. This may lead to an underestimation of rCBV in the larger vessels with the dynamic method (24).

In our study, the FLASH measurements showed smaller signal changes than the EPI data due to the shorter echo time. In addition, the signal-to-noise ratio in FLASH (SNR 75) was decreased compared with EPI (SNR 145) due to the lower flip angle and the higher spatial resolution. As a result, the FLASH data showed a considerably lower effect-to-noise ratio than the EPI data, which reduced the pointwise correlation between the static and the dynamic method for the FLASH data.

In the ROI analysis, the main difference between the FLASH and the EPI data is the relatively lower rCBV in the deep gray matter structures determined by the FLASH measurements (Table 1). The main reason for this discrepancy is probably the different number of slices. Unlike the multi-slice EPI scans, the FLASH data are single slice only, and the rCBV values cannot be interpolated in the slice direction during coregistration with the high-resolution anatomical scan. In addition, since only a small part of the deep gray matter structures is covered by the FLASH images, the rCBV in this area may be systematically different from the rCBV in the whole deep gray matter complex covered by the EPI technique. The larger slice thickness of the FLASH scans also causes more volume averaging with the surrounding lower white matter rCBV values. Overall, the gray-to-white and gray-to-deep gray matter rCBV ratios are in agreement with previously published data (24–26).

FLASH showed a better agreement between the static and dynamic ROI values than EPI. With EPI, the rCBV values in the deep gray and the gray matter were slightly lower with the static method than with the dynamic method, while FLASH showed no differences between the two processing methods (Fig. 4). These lower deep gray and gray matter values for the static method with the EPI data suggest a non-linear relationship between the two methods. This effect may occur because our EPI measurements had a longer echo time and thus larger signal changes compared with FLASH. However, compared with a linear regression, a second order regression analysis did not significantly improve the regression results or the sum of the squares of the difference between the data points and the regression values. This may be due to the very high density of data points in the region of the gray and white matter values, dominating the regression results (Fig. 3). An additional source of differences between the FLASH data and the EPI data may be the change in T1 that is induced by the contrast agent. However, a change in T1 would most strongly affect the FLASH results, causing an underestimation of the higher rCBV values.

Another possible disparity between the static and dynamic rCBV data may be due to the use of a tracer that is not truly intravascular. The pharmacokinetics of low-molecular-weight Gd contrast agents typically show a fast initial decay (time constant ~7 min) of the blood concentration due to the bio-distribution into the inner organs and muscles. During the later phase, a slower decay (time constant ~90 min) is observed that corresponds to the washout through the kidney (27). Therefore, the effect-to-noise ratio of the static method can be expected to decay rapidly during the first few minutes after contrast agent administration. The concentration changes, however, are small during the acquisition of one time point (2.5 sec), and the washout should affect all voxels in the brain equally if the BBB is intact. The sensitivity of the two methods is essentially determined by the amount of signal change, which in turn reflects the concentration of the contrast agent in the blood, and the acquisition time. Because of the higher concentration during the first pass, the dynamic method should be more sensitive than the static method. However, the development of true intravascular tracers (12,13,28–32) will make it possible to maintain a high blood concentration for a sustained period and thus will enable the measurement of high-resolution rCBV maps with the static method. The static rCBV maps may be acquired during a steady contrast agent concentration and thus may avoid the acquisition during the first recirculations. In addition, other contrast mechanisms, such as the change in T1 relaxivity, may be exploited; these mechanisms currently suffer from low signal changes (24,33,34).

Both the static and dynamic methods used in this study can be optimized further. The reproducibility and sensitivity of the dynamic method might be even higher if an automatic injector with a higher injection rate is used. The static method could be improved further by the use of an intravascular tracer. Thus, the static method in the current study is only an approximation of the effects of a true intravascular tracer with a steady concentration. However, the results obtained using both methods on the same data sets indicate that it is possible to obtain comparable rCBV maps with either method.

Our study suggests that the effect-to-noise ratio of dynamic rCBV measurements may be improved by combining the static and dynamic methods. Such an approach may model the entire signal time course, including the dynamic bolus phase and the signal decrease in the later phase, to obtain rCBV maps with higher effect-to-noise ratios.

## CONCLUSIONS

Our study demonstrates that it is possible to obtain rCBV maps of the entire brain, without the necessity for ultra-fast imaging, by utilizing the signal changes before and after contrast agent administration. The results of the static and the dynamic methods are in good agreement. With the development and clinical introduction of true intravascular tracers, it will be possible to generate high-resolution rCBV maps using the static effect.

## ACKNOWLEDGMENTS

This study was supported in part by the NIH (Scientist Development Award for Clinicians DA 00280, to L.C.), the State of California Universitywide AIDS Research Program to UCLA Care Center (CC97 LA 175), and the French Association for Cancer Research (for E.I.).

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