Quantification of Blood Flow in Brain Tumors: Comparison of Arterial Spin Labeling and Dynamic Susceptibility-weighted Contrast-enhanced MR Imaging

PURPOSE: To implement an arterial spin labeling technique that is feasible in routine examinations and to test the method and compare it with dynamic susceptibility-weighted contrast material–enhanced magnetic resonance (MR) imaging for evaluation of tumor blood flow (TBF) in patients with brain tumors.

MATERIALS AND METHODS: Thirty-six patients with histologically proven brain tumors were examined at 1.5 T. A second version of quantitative imaging of perfusion by using a single subtraction with addition of thin-section periodic saturation after inversion and a time delay (Q2TIPS) technique of pulsed arterial spin labeling in the multisection mode was implemented. After arterial spin labeling, a combined T2- and T2*-weighted first-pass bolus perfusion study (gadopentetate dimeglumine, 0.2 mmol/kg) was performed by using a double-echo echo-planar imaging sequence. In regions of interest, maps of absolute and relative cerebral blood flow were computed and analyzed with arterial spin labeling and dynamic susceptibility-weighted contrast-enhanced MR imaging, respectively.

RESULTS: Both techniques yielded the highest perfusion values in imaging of glioblastomas and the lowest values in imaging of two low-grade gliomas that both showed strong gadopentetate dimeglumine enhancement. There was a close linear correlation between dynamic susceptibility-weighted contrast-enhanced MR imaging and arterial spin labeling in the tumor region of interest (linear regression coefficient, \( R = 0.83; P < .005 \)). Blood flow is underestimated with arterial spin labeling at low flow rates. High- and low-grade gliomas can be distinguished at the same level of significance with both methods. Absolute TBF is less important for tumor grading than is the ratio of TBF to age-dependent mean brain perfusion.

CONCLUSION: Arterial spin labeling is a suitable method for assessment of microvascular perfusion and allows distinction between high- and low-grade gliomas.

Tumors of glial origin are among the most frequent primary brain tumors. Different classifications have been proposed for subcategorization of gliomas into two, three, or four classes of tumors of increasing malignancy and biological aggressiveness (1–3). Most low-grade gliomas progress in malignancy (ie, they undergo malignant transformation). Angiogenesis has a key role both in the development and in the malignant transformation of tumors. Without the formation of the blood vessels that supply blood to the tumor, a tumor can only grow to a size of 1–2 mm in diameter, and for growth to this size, the tumor is supplied with energy by diffusion (4). Much current research focuses on the development of antiangiogenic treatment strategies. Monitoring of such therapies requires diagnostic procedures for the quantitative assessment of vascularization in vivo.
Conventional magnetic resonance (MR) imaging allows assessment of glioma morphology, and the administration of gadolinium-based contrast media enables specific identification of areas with a disrupted blood-brain barrier. In general, the extent of blood-brain barrier disruption in gliomas increases with malignancy. However, high-grade gliomas may not show contrast enhancement, whereas some low-grade tumors are characterized by pronounced extravasation (5,6). Although the contrast enhancement provides information about blood-brain barrier disruption and vessel permeability of the tumors, nondynamic MR imaging studies do not yield precise information about tumor angiogenesis that occurs at the capillary level, let alone quantitative data.

Cerebral perfusion is typically determined by using dynamic susceptibility-weighted contrast material–enhanced MR imaging with echo-planar MR imaging sequences. This technique allows simultaneous measurement of cerebral blood flow (CBF), cerebral blood volume (CBV), and vessel permeability in the presence of a disrupted blood-brain barrier in several sections (7–11). Although bolus-tracking methods initially only allowed determination of relative CBF and relative CBV, findings in a recently reported validation study with positron emission tomography as a reference produced reasonable absolute values for CBF (12). Vascularization factors that are thus determined correlate with both histologic tumor grade and individual histologic features such as mitotic activity (11,13,14).

Both gradient-echo (GRE) and spin-echo echo-planar MR imaging are commonly used in first-pass bolus studies. Changes in relaxation times caused by contrast agents depend on mean vessel diameter and are different for change in R2, or ΔR2, and change in R2*, or ΔR2* (15). The results of a study suggest that GRE-determined relative CBV and the ΔR2/ΔR2* ratio seem to be most appropriate for the evaluation of tumor angiogenesis (16).

Another method for determining CBF is arterial spin labeling. With arterial spin labeling, water is used as a freely diffusible intrinsic tracer. Arterial blood outside the imaging section is labeled by an inversion pulse. After a transit time from the labeling region to the imaging section, blood spins exchange with tissue water at the capillaries. Subtraction of a control image without prior labeling leaves the transported magnetization only, and this process results in a perfusion-weighted image. CBF can be quantified by using the general kinetic model, an adaptation of the Kety model to arterial spin labeling, of Buxton et al (17). The experience gained with arterial spin labeling in brain tumors so far is limited (18,19). The purpose of our study was to implement an arterial spin labeling technique that is feasible in routine examinations and to test the method and compare it with dynamic susceptibility-weighted contrast-enhanced MR imaging for evaluation of tumor blood flow (TBF) in patients with brain tumors.

**MATERIALS AND METHODS**

### Patient Population

Thirty-six consecutive patients with histologically proven gliomas (n = 29) or metastases (n = 7) were included in the study. Tumors that had been treated before were included if they showed definitive signs of residual or recurrent tumor at conventional MR imaging. All tumors were classified according to the revised World Health Organization brain tumor classification (1). Tissue for histologic analysis was obtained at stereotactic biopsy (11 patients) or during surgical resection of the tumor. The study was approved by the institutional review board of Charité Medical School, Berlin, Germany, and informed consent was obtained from all patients. Twelve of the 29 patients with glioma had low-grade (World Health Organization grades I and II) gliomas; 17 had high-grade (World Health Organization grades III and IV) gliomas. Ten patients with gliomas had undergone treatment at the time of the perfusion studies. Irradiation was performed in two patients. Surgery was performed in the other eight patients, and three of the patients underwent additional chemotherapy, whereas four patients underwent irradiation. Two of the metastases had been treated before, one with stereotactic irradiation and one with surgery and subsequent chemotherapy.

### Imaging Protocol

All MR imaging examinations were performed with a clinical 1.5-T imaging unit (Magnetom Vision; Siemens, Erlangen, Germany). Motion artifacts were prevented with fixation of the patient’s head in the head coil with a vacuum cushion.

**Anatomic images.** The MR examination began with the acquisition of anatomic images of the whole brain by using double-echo intermediate-weighted T2- and T1-weighted sequences with the following parameters: sections, 21; thickness, 5 mm; field of view, 230 mm; and matrix, 256 × 256. With T2-weighted sequences, parameters were as follows: repetition time msec/echo times (TEs) msec, 3,800/22, 90, with a 90° flip angle. With T1-weighted sequences, the parameters were as follows: 735/14, with a 70° flip angle. Tumor regions were identified on the T2-weighted images, and the central tumor section was chosen for the perfusion studies.

**Arterial spin labeling imaging.** Perfusion imaging was performed by using a second version of quantitative imaging of perfusion by using a single subtraction with addition of thin-section periodic saturation after inversion and a time delay (Q2TIPS) tagging scheme, which is a pulsed arterial spin labeling method that enables acquisition of multiple sections (20). In the Q2TIPS technique, the time delay after inversion is called T1, and may be referred to as τ. After the section-selective and nonselective inversion pulse and a time delay τ, the trailing edge of the tagged bolus was cut off by a train of regional saturation pulses (Fig 1). Thus, a sharply defined blood bolus of temporal length was produced. If the imaging section is acquired after T1 = τ + Δt, where Δt is the maximum transit time within the section, the resulting difference image is a quantitative perfusion image.

Section-selective and nonselective inversion was accomplished by using hyperbolic secant pulses of variable bandwidth and shape (21). For the 35-mm inversion slab that was used in most cases, a 10,240-μs pulse of shape \( B_1(t) = \text{sech}(\beta \cdot t) \) and a frequency offset of \( \Delta \omega(t) = -\mu \cdot \beta \cdot \tanh(\beta \cdot t) \), where \( \Delta \omega(t) \) is expressed in rads per second, with \( \beta = 1,200 \) and \( \mu = 18 \), were chosen. Multisection perfusion imaging was performed by using a single-shot echo-planar imaging readout. Imaging parameters were as follows: repetition time msec/TE msec/T1s msec, 3,700/29 (asymmetric echo)/1,300, 1,430, and 1,560 (for sections 1–3, respectively); sections, three; section thickness, 8 mm; intersection gap, 3 mm; τ, 1,200 msec; Q2TIPS saturation length, 100 msec; saturation slab thickness, 40 mm; matrix, 128 × 128; interpolated to 256 × 256; field of view, 230 mm; bandwidth, 1,250 Hz/pixel; signals acquired, 50; and total acquisition time, 6 minutes 10 seconds. For quantification, single-shot echo-planar MR im-
Dynamic susceptibility-weighted contrast-enhanced MR imaging.—First-pass bolus MR imaging was performed next by using the same section orientations and thicknesses as were used for arterial spin labeling. At least one section was positioned at the level of the middle cerebral artery to obtain the arterial input function; one or more sections were added if none of the sections used at arterial spin labeling contained the middle cerebral artery. A loading dose of 0.1 mmol/kg was administered to diminish T1-shortening effects in case of blood-brain barrier disruption, and dynamic MR imaging was then performed afterward by using a single-shot double-echo echo-planar MR imaging sequence. After a 90° excitation pulse, a GRE echo-planar MR image was acquired first. Following a 180° section-selective refocusing pulse, a spin-echo echo-planar MR image of the same section was recorded. The TE for the GRE and spin-echo MR images was 35 and 105 msec, respectively. Three sections with 80 images were acquired with a repetition time of 1 second. Five seconds after imaging was started, 0.2 mmol/kg of gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) was administered by using a power injector (Spectris; Medrad, Volkach, Germany) at a flow rate of 5 mL/sec when possible.

Postcontrast imaging.—Transverse and coronal T1-weighted MR images were acquired by using the same parameters as were used to obtain the anatomic images. When patients underwent subsequent radiation therapy, a high-spatial-resolution three-dimensional turbo fast low-angle shot sequence (magnetization-prepared rapid acquisition GRE sequence) was acquired instead, and transverse images were reconstructed from that data set.

Since all perfusion studies were performed by using echo-planar data acquisition, image quality was reduced in regions with susceptibility artifacts at bone-air interfaces (eg, the petrous temporal bone, the paranasal sinuses, and the skull base). Such artifacts can be reduced by using thinner sections, but the signal-to-noise ratio decreases accordingly. Because we used 8-mm sections for reasons pertaining to the signal-to-noise ratio, our acquisitions were affected by signal dropouts in some regions of the brain. However, none of the tumors studied were markedly distorted. All patients tolerated the examinations without any adverse reaction to the injection of a bolus of contrast material.

Data Processing.

Images.—All images were transferred to a personal computer workstation and analyzed by using customized noncommercial software.

Quantification of images obtained with arterial spin labeling.—With the assumption that a fast and complete exchange of blood and tissue spins has occurred, CBF in a voxel can be quantified (17,20) according to the following equation:

\[ f = \frac{\Delta M(TI)}{2 \cdot M_{0B} \cdot T_e \cdot e^{\frac{-T_1B}{TE}} \cdot q(TI)} \]

where \( f \) is the blood flow; \( \Delta M(TI) \) is the signal difference measured at time TI after labeling; \( M_{0B} \) is the signal of a voxel containing 100% blood in thermal equilibrium, which has to be acquired separately but within the sequence; \( T_1B \) is the constant relaxation time of arterial blood; and \( q(TI) \) is a factor to correct for the difference between blood and tissue T1 and venous outflow. For gray and white matter and the timing of our sequence, \( q \) is approximately 0.85. In our study, a \( T_1B \) of 1,200 msec was assumed. The signal \( M_{0B} \) of a voxel containing 100% fully relaxed blood depends on receiver adjustment and the readout module used. It cannot be determined directly from the \( M_0 \) images, as partial-volume and flow effects hinder the selection of a single voxel within a large vessel. We used the method described by Wong et al (22) to estimate \( M_{0B} \) from the measured signal of white matter, or WM, indicated as \( M_{0WM} \) in a region of interest. By using the proton density ratio, which is called \( A \), between blood and white matter, the \( T_2^* \) (GRE echo-planar MR imaging), and the TE of our sequence, \( M_{0B} \) is calculated as follows:

\[ M_{0B} = A \cdot M_{0WM} \cdot e^{1/T_2^*WM - 1/T_2^*/TE}. \]

With a proton density ratio of 1.06, \( T_2^* \) values of 55 msec for white matter and 100 msec for blood, and our TE of 29 msec, \( M_{0B} \) equals 1.34 \( \cdot M_{0WM} \).

Processing of dynamic MR images.—Dynamic susceptibility-weighted contrast-enhanced MR images were postprocessed by using singular value decomposition and deconvolution as described by Ostergaard et al (23). Measured signals, \( S(t) \), were converted to relative concentration time courses, \( c(t) \), in a voxel-by-voxel manner by using the mean baseline signal, \( S_0 \), with the following equation:

\[ c(t) = -1/TE \ln[S(t)/S_0]. \]
pending on the contrast-to-noise ratio of the measurement. Relative CBF, relative CBV, and mean transit time maps were generated voxel by voxel from the maximum of the deconvolved function, numerical integration of \( c(t) \), and the ratio of relative CBV to relative CBF, respectively. Apart from the administration of a loading dose of 0.1 mmol gadopentetate dimeglumine, no correction for contrast agent extravasation was performed, which resulted in an underestimation of relative CBV values in case of further accumulation. Although this is not state-of-the-art data analysis, there is little effect on computed relative CBF values, and these values were the focus of our investigations.

Region of interest analysis.—Six regions of interest per section were placed by one of the authors (C.W.), who was not blinded to the diagnosis, as follows: tumor, determined as enhancement on T1-weighted postcontrast images; a circular region of interest of 27 voxels in the apparent maximum TBF region; white matter; gray matter; contralateral hemisphere, excluding tumor if any; and contralateral mirrored tumor region of interest. Five factors were determined in these regions of interest as follows: absolute CBF, determined with arterial spin labeling, and relative CBF and relative CBV, determined with GRE and spin-echo dynamic susceptibility-weighted contrast-enhanced MR imaging.

Statistical Analysis

Statistical analysis was performed by using software packages (SPSS, SPSS, Chicago, Ill; Origin, Microcal, Northampton, Mass). For comparison of the methods in terms of TBF, the ratios of TBF to mean CBF determined by using arterial spin labeling and GRE dynamic susceptibility-weighted contrast-enhanced MR imaging were analyzed in all patients. A Durbin-Watson residual test was performed to identify outliers. Linear regression analysis was performed on the data to determine the regression line and the linear regression coefficient. A nonparametric Mann-Whitney rank test was used to analyze the relationship between histologically determined tumor grade and the measured perfusion values and ratios. Findings were considered to indicate a significant difference with a \( P \) value of less than .005.

To determine the correlation between

### Results of Perfusion Measurements in 36 Patients

<table>
<thead>
<tr>
<th>Patient No./Sex/Age (y)</th>
<th>Histologic Diagnosis and World Health Organization Grade</th>
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Note.—GRE MR imaging is gradient-echo dynamic susceptibility-weighted contrast-enhanced MR imaging.

* Both TBF and CBF are relative values. ND = no data (ie, data missing due to patient noncompliance, such as patient movement).

† TBF is expressed as milliliters per 100 g multiplied by minutes.
the different methods in general, a voxelwise data analysis of all three CBF maps (ie, with scatterplots and linear regression analysis) was performed intraindividually in selected patients, preferably in young patients who had a good overall perfusion state.

RESULTS

The Table summarizes the patient data, histopathologic diagnoses, and measured CBF values. Note that the Table does not include results of the spin-echo studies. Relative CBF ratios determined by using either GRE or spin-echo dynamic MR imaging were closely correlated, which is a finding that is in agreement with the results of other investigators (24).

The absolute TBF values determined by using arterial spin labeling ranged between 32 mL/100 g · min in a World Health Organization grade I tumor (ganglioglioma) and 227 mL/100 g · min in a brain metastasis of an unknown primary tumor. In untreated low-grade gliomas (World Health Organization grades I and II), absolute TBF ranged from 32 to 65 mL/100 g · min, with a mean of 47 mL/100 g · min; in high-grade gliomas (World Health Organization grades III and IV), absolute TBF ranged from 63 to 208 mL/100 g · min, with a mean of 116 mL/100 g · min. Since no calibration of the first-pass bolus data was performed, relative TBF is presented as the ratio to the mean relative CBF of the particular section, which is determined as the mean of all voxels of the contralateral hemisphere. Thus, each ratio is intraindividual. Directly comparable ratios of absolute TBF to absolute CBF, determined with arterial spin labeling, were computed in the same way. The mean GRE TBF/CBF ratios in untreated low-grade gliomas and in high-grade gliomas were 0.60 and 1.28, respectively; arterial spin labeling yielded TBF/CBF ratios of 0.64 and 1.54, respectively. None of the untreated low-grade gliomas had a TBF/ CBF ratio with arterial spin labeling that was greater than 0.85; no high-grade glioma had a ratio that was less than 0.97. Both groups were less clearly distinguished in terms of the absolute TBF and the GRE TBF/ CBF ratio. Although we administered a loading dose of contrast agent, low and negative values of relative tumor blood volume (TBV) were measured in strongly enhancing tumors (data not shown). We compensated for this discrepancy by restricting numerical integration of the relative concentration time curves to the first pass of the bolus, but the problem remained in principle.

Both mean CBF and white matter blood flow show large interindividual variation and significant decrease with age. The age-related reduction of CBF has different effects on the two imaging tech-
niques. Figure 2 shows a comparison of the results obtained with arterial spin labeling and GRE dynamic susceptibility-weighted contrast-enhanced MR imaging performed in a young patient and in an older one. There is, above all, a decrease in signal-to-noise ratio with the arterial spin labeling method in older patients, and this decrease is caused by the prolonged transit time of the blood from the labeled region to the imaging section. Longer circulation and transit times pose no problem with bolus tracking, a method that yields perfusion images of similar quality in older patients as well.

Figures 3 and 4 present the results of the perfusion studies as box plots. In Figure 3, absolute TBF values are shown in relation to the TBF/CBF ratios, both of which were obtained with arterial spin labeling and were scaled to have identical maximum and identical minimum values. Representation of TBF in relation to the individual patient’s perfusion reduces the scatter within groups and results in a better discrimination. Figure 4 shows the tumor-brain ratios of TBF and TBV as measured with arterial spin labeling and GRE first-pass bolus MR imaging. All values clearly show the perfusion differences between high- and low-grade gliomas, as well as the decreased tumor perfusion after treatment.

For practical diagnostic purposes, results of both perfusion studies provided important additional information in many of the tumors investigated and resulted, for instance, in a revised in vivo assessment of malignancy compared with findings at conventional nondynamic MR imaging. Figure 5 shows an atypical glioblastoma with only weak contrast agent enhancement. Perfusion imaging, however, revealed high TBF, a specific indicator of a high-grade glioma; this tumor was confirmed with histologic analysis. In contrast, Figure 6 shows a tumor that was primarily diagnosed as a glioblastoma because of strong contrast agent enhancement. However, blood flow was markedly decreased in the tumor, and this finding suggested a low-grade tumor (ganglioglioma). Both methods also provide information for in vivo assessment of tumor malignancy of different areas within the same tumor. Figure 7 depicts a glioblastoma that shows heterogeneous vascularization. In this case, central parts of the tumor have very high blood flow, whereas perfusion in the occipital part is low. This information is important for choosing the most malignant parts of the neoplasm for biopsy.

Statistical analysis demonstrated a number of significant differences between groups. Untreated high- and low-grade gliomas differed significantly in terms of absolute TBF, as well as in the ratios of TBF to mean CBF and white matter flow, determined with arterial spin labeling. The ratios were likewise significantly different when determined with the first-pass bolus method. Here, the blood volume ratios of tumor to brain and tumor to white matter were also of significance. Furthermore, a number of factors

**Tumor Classification**

**Figure 4.** Box plot shows relative TBF and relative TBV values determined by using arterial spin labeling (white bar) and GRE dynamic susceptibility-weighted contrast-enhanced MR imaging (TBF, light gray bars; TBV, dark gray bars) in relation to the respective mean values in the contralateral hemisphere. Relative TBF and TBV are highest in untreated high-grade gliomas. Perfusion difference between untreated low-grade gliomas and high-grade gliomas was statistically significant ($P < .001$), as was that between treated and untreated high-grade gliomas. Keys are the same as for Figure 3.

**Figure 5.** Patient 19. Glioblastoma in a 51-year-old woman.
A, Transverse T2-weighted MR image (3,800/90). B, Contrast-enhanced T1-weighted MR image (735/14; flip angle, 70°) shows atypical weak enhancement (arrowheads). C, Blood flow map obtained with GRE dynamic susceptibility-weighted contrast-enhanced MR imaging shows two foci of high TBF (arrowheads). D, Perfusion image obtained with arterial spin labeling shows the two foci that are in C as less apparent. Foci may represent large vessels within the tumor.
showed a significant reduction of tumor perfusion in high-grade gliomas after treatment. Here again, both absolute flow values and the ratios of TBF and TBV to brain and white matter were significantly reduced. In low-grade gliomas before and after treatment, significant differences were observed only in the ratios of TBF and TBV to those of white matter (ie, with arterial spin labeling, as well as with GRE dynamic susceptibility-weighted contrast-enhanced MR imaging). The number of patients with metastases was too small for statistical analysis.

Figure 8 shows a scatterplot of TBF ratios in all patients determined by using arterial spin labeling and GRE bolus tracking. One outlier (patient 33) was identified by using the Durbin-Watson test and had a standardized residual of 3.56, which was well outside the gaussian residual distribution. As seen on images obtained with the contrast-enhanced three-dimensional turbo fast low-angle shot sequence, this metastasis was supplied by a large artery and had direct venous drainage into the transverse sinus, which led to a short transit time and very high blood flow. There was a close correlation between both methods, with a linear regression coefficient of \( R = 0.83 \) (\( P < .001 \)) if the outlier was eliminated. The slope of the regression line was 1.04 with an intercept of 0.09, and these values were in agreement with the expected identity with a \( P \) value of less than .05. However, TBF ratios determined by using the two methods showed marked deviation at high flow, with values determined with arterial spin labeling being higher than those determined with first-pass bolus MR imaging. Forcing the regression line through the origin resulted in a slope of 1.14, with a 95% CI ranging from 1.01 to 1.26. Inclusion of patient 33 in the calculation profoundly affected the regression line, which still yielded an \( R \) of 0.82 but a slope of 1.30 with an intercept at \(-0.06\).

For a direct comparison of CBF determination by using arterial spin labeling and GRE and spin-echo dynamic susceptibility-weighted contrast-enhanced MR imaging, CBF values were analyzed in a voxel-by-voxel manner, and linear regression was performed in all individual sections of selected patients. The calculation included only voxels that could be analyzed in all three studies. Correlation was best between GRE and spin-echo dynamic susceptibility-weighted contrast-enhanced MR imaging, with a linear regression coefficient of \( R = 0.83 \). Regression coefficients determined with arterial spin labeling and either GRE or spin-echo bolus tracking differed significantly in about two-thirds of all sections, but there was no general tendency for a better correlation of the maps obtained with arterial spin labeling than with the maps obtained with either of the respective dynamic methods. Rather, we found different correlations in adjacent sections in the same patient. The mean \( R \) obtained with arterial spin labeling and spin-echo dynamic susceptibility-weighted contrast-enhanced MR imaging was 0.33, and that obtained with arterial spin labeling and GRE dynamic imaging was 0.35. This difference was not statistically significant. The histograms of the individual maps showed broadening of the arterial spin labeling distribution because of the lower signal-to-noise ratio but no obvious difference in shape. In turn, there was no dependency on the arterial spin labeling section number, which deter-
mines the inversion and transit time in a multisection acquisition, in the sequence.

**DISCUSSION**

Our results showed that there is a close correlation between arterial spin labeling and first-pass bolus methods in the determination of blood flow in brain tumors. Both techniques demonstrated the highest TBF values in patients with glioblastomas and metastases and were able to show heterogeneous blood flow distribution within an individual tumor.

Perfusion imaging in brain tumors has important clinical and diagnostic implications. We could show that perfusion imaging by using arterial spin labeling allows reliable differentiation between low-grade and high-grade gliomas, as has been shown by other investigators with different perfusion imaging techniques (14,16). Absolute flow rate is not a crucial factor for tumor grading; it has to be corrected for age- and patient-dependent mean brain perfusion. By using the resulting ratios, arterial spin labeling and dynamic susceptibility-weighted contrast-enhanced MR imaging are equally good. However, only arterial spin labeling yields absolute values, and this determination of absolute values allows comparison of patients with each other or comparison of values that may be obtained during the course of treatment in individual patients. Bolus-tracking examinations often rely on relative parameters, such as the ratio of TBF to perfusion in white matter, and this ratio showed wider scatter in our investigation. This is not surprising, because ratios incorporate the measurement errors of both values. The slight superiority of arterial spin labeling in the differentiation between tumor groups should not be overrated, since the study was not conducted in a blinded fashion. Definition of the tumor region of interest could have been biased by the knowledge of tumor type and World Health Organization grade in case of weak or absent enhancement. Here, the region of interest of the suspected tumor had to be defined. A nonblinded examiner is more likely to include voxels that match the expected tumor perfusion. Among the 36 patients, five tumors showed weak enhancement.

With the rule of thumb, mean TBF of low-grade gliomas is less than the mean CBF; that of high-grade gliomas is greater than the mean CBF. This rule is important, since the proportion of nonenhancing high-grade gliomas seems to be higher than has been assumed so far. The malignancy of such nonenhancing malignant gliomas is typically underestimated on the basis of conventional MR imaging findings, and this underestimation may lead to wrong therapeutic decision making.

The weighting of the perfusion image obtained with arterial spin labeling depends on the timing of the sequence. In older patients, in whom lower perfusion leads to longer transit times, the distal end of the labeled bolus does not reach the capillary bed, and part of the blood is still contained in the arterial vessels. Since no crusher gradients are used for suppressing the arteries, the latter appear in the perfusion image. As the TI of the spin labeling sequence increases, there is a shift in the perfusion image toward the microvasculature. With a change in the timing parameters of the arterial spin labeling sequence, the examiner can choose the vascular level at which imaging takes place, that is, whether arterial or capillary blood predominates. However, this limits the applicability of the theoretical model of quantification, a model that is based on the assumption that all labeled blood is within its target voxel at the time of acquisition. The flexibility of the arterial spin labeling technique allows individual adjustment of acquisition to answer specific questions. In a study by Donahue et al (16), the relative CBV values determined with spin-echo imaging did not correlate with tumor grades, whereas those determined with GRE did. It might thus be possible to improve tumor grading by means of emphasis on the arterial tumor vessels with selection of a short TI and no application of crusher gradients.

Arterial spin labeling has the advantage of being noninvasive and does not require administration of an extrinsic tracer. Hence, no contrast medium affects the physical, chemical, or physiologic properties of the blood. The perfusion-weighted difference image is available immediately after acquisition with only minimal postprocessing, and this availability is a clear advantage in a routine clinical setting. The arterial spin labeling method allows reliable absolute quantification, which is not affected by a disrupted blood-brain barrier. The contrast medium–based technique is superior in that it yields perfusion maps with a far better signal-to-noise ratio and allows acquisition of a larger number of sections. Moreover, not only can TBF be determined but also TBV and vessel permeability as well. Findings of recent studies show that information about vessel permeability may contribute to the characterization and grading of gliomas (13). Although attempts have been made to determine CBV and even the oxygen extraction fraction with arterial spin labeling techniques, the acquisition times are much too long to be feasible in practice (25).

Accurate quantification of CBF by using arterial spin labeling depends on arterial transit times to the voxels, local relaxation times of the tissue, and equilibrium magnetization of the blood. The general kinetic model is based on the as-

![Figure 8. Scatterplot shows ratios of TBF to mean CBF in the contralateral hemisphere of the section determined with spin labeling and bolus tracking in all 36 patients. Linear regression analysis excluding the marked outlier (circled square) reveals a high correlation, with $R = 0.83$ and $y = 0.09 + 1.04x$, for the regression line, which is not statistically different from identity at a $P$ value of less than .05.](image-url)
assumption that there is complete exchange of labeled blood and tissue spins. This assumption does not hold at extremely high flow rates (eg, in rats), but the model accurately represents physiologic flow rates in humans (26).

Transit time certainly has the most pronounced effect on the accuracy of quantification. Transit times range between 200 and 400 msec in gray matter and between 700 and 1,000 msec in white matter (27). The acquisition parameters we used were chosen with regard to a maximal difference signal. For long transit times, as in white matter, perfusion is underestimated, especially in patients with an already low overall perfusion. The calculated flow probably best matches actual flow in gray matter. Arterial spin labeling is therefore more suitable for assessment of hypervascularized lesions, whereas it has a higher error rate in assessment of hypovascularized abnormalities.

Additional systematic errors result from the assumption of a constant T1 relaxation time of arterial blood irrespectively of vessel size and blood oxygenation. The same holds true for T2*. In Equation (1), a constant T2* of the labeled blood spins is assumed at all times of the measurement—that of arterial blood. If blood spins leave the capillaries and exchange with the tissue, T2* of that part of the label also changes to that of the tissue. For an extraction fraction, E, the actual blood flow, or \( f \), is then underestimated by a factor that is determined with the following equation:

\[
\frac{f_m}{f} = (1 - E) + E \cdot e^{\frac{T2*}{1/T2* - 1/T2f}},
\]

where \( f_m \) is the measured blood flow and T2*\(_a\) and T2*\(_f\) are the relaxation times of blood and tissue, respectively. For white matter with an assumed T2* of 55 msec, blood flow is underestimated by approximately 20% if all of the labeled spins have left the capillaries at the time of measurement. In general, brain tumors show prolonged T2* values; therefore, the error is accordingly smaller. In the dynamic susceptibility-weighted contrast-enhanced MR imaging measurement, different T2 and T2* values are included in the baseline signal of every voxel, and, therefore, they are corrected when relative concentration is calculated by using Equation (3).

The quantification model used in bolus tracking is based on the assumption that the contrast medium is kept within the vessels. Extra adjustment is required to correct for extravasation, which occurs in the majority of tumors.

Quantitative determination by using the dynamic susceptibility-weighted contrast-enhanced MR imaging technique crucially relies on the selection of the proper arterial input function. The selection of such voxels is typically performed manually, although automated algorithms can be used to label candidate voxels. Thus, the arterial input function depends on not only the examiner but also section positioning. It is assumed that the arterial input function is identical for all voxels, but there may be voxels that represent several feeding arteries with different arrival times of the contrast medium bolus. Measurements may be rendered useless by strong patient movement and, unlike measurements obtained with arterial spin labeling, they are very difficult to repeat.

Linear regression analysis showed a very good correlation between arterial spin labeling and first-pass bolus perfusion imaging for determination of the ratio of TBF to mean CBF, with an R of 0.83 and a slope of the regression line of 1.04. However, for high TBF values, the tumor-brain blood flow ratios determined by using arterial spin labeling were markedly greater than those obtained with dynamic susceptibility-weighted contrast-enhanced MR imaging. This is probably caused by the underestimation of perfusion in voxels with long transit times, as already described, that are included in the calculation of the mean CBF. This general disadvantage of the arterial spin labeling technique can only be overcome with a longer delay of acquisition after labeling, which would decrease the signal-to-noise ratio of the perfusion study. A signal-to-noise ratio improvement is only expected from use of higher field strengths (eg, 3 T) or of receive coils with an improved sensitivity.

In conclusion, our results show that arterial spin labeling and dynamic susceptibility-weighted contrast-enhanced MR imaging are suitable methods for the characterization and grading of tumors. Both techniques show the heterogeneous vascularization within a tumor and can help distinguish high-grade from low-grade gliomas.

Important practical advantages of the arterial spin labeling technique are the immediate availability of perfusion images and the ease of quantification without extensive postprocessing. Perfusion data can be obtained in a flexible manner (eg, without the necessity to prepare a power injector) and can be integrated into a conventional MR imaging examination at any time as long as no contrast agent has been administered. Arterial spin labeling is especially suitable for examination of children who are often frightened and may require sedation before a bolus of contrast medium can be injected. The high perfusion and short blood circulation times in young patients result in a fairly good signal-to-noise ratio with the arterial spin labeling studies. All of these features make this technique a suitable candidate for the diagnostic assessment of patients with brain tumors and other brain disorders associated with changes in vascularization.

References
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