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Comparison of Gradient- and Spin-Echo Imaging: CBF, CBV, and MTT Measurements by Bolus Tracking

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The authors measured cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) in pigs by gadodiamide bolus injections and the bolus tracking technique. Two different pulse sequences were applied and compared: gradient-echo (GE) and spin-echo (SE) echoplanar imaging (EPI). After normalization of CBF and CBV values to the area under the arterial input function (AIF), a linear relation between the two methods was found, suggesting that a previous normalization approach for determining absolute CBF by SE EPI may be extended to GE EPI measurements. The ratio between CBV values measured with GE and SE [CBV (GE)/CBV (SE)] was 2.96. Assuming that the GE acquisition reflects total CBV, our findings suggest that SE is sensitive to 34% (1/2.96) of the total vasculature. The corresponding ratio for CBF was 2.53. There was no significant difference in these two ratios, suggesting that MTT estimates derived from GE and SE EPI measurements are comparable. The findings suggest that SE and GE are equally useful in clinical measurements of functional parameters such as CBF, CBV, and MTT in the brain. J. Magn. Reson. Imaging 2000;12:411–416. © 2000 Wiley-Liss, Inc.

Index terms: spin echo; gradient echo; MRI; dynamic susceptibility contrast imaging; perfusion; CBF

WHEN STUDYING cerebrovascular diseases such as stroke and migraine, pathophysiological changes are often quantified in terms of the functional parameters cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT). The determination of these parameters requires rapid, dynamic MR imaging during bolus injection of susceptibility contrast agent. Two echoplanar imaging (EPI) sequences are typically used in this context: gradient-echo (GE) or spin-echo (SE) EPI.

GE is often used in a clinical environment due to better coverage of the brain; given the same repetition time, it is possible to obtain more slices during a single acquisition. Furthermore, due to the susceptibility contrast sensitivity of GE sequences, the contrast dose used in the GE experiment is typically only half of that used for SE. On the other hand, the SE sequence has the inherent advantage of being weighted toward the microvasculature (1,2) making it particularly useful in depicting morphologic or functional changes specific to the microvasculature, eg, angiogenesis (3) or capillary deoxygenation in functional magnetic resonance imaging (fMRI) (4). In cerebrovascular disease, regulatory mechanisms are typically believed to occur on a capillary or arteriolar level, again favoring SE as the method of choice for studying these diseases. Furthermore, due to a lesser sensitivity to differences in magnetic susceptibility at air-tissue interfaces, SE offers better anatomic precision and detail in clinical studies.

Given the advantages of GE EPI, we wished to investigate whether the two pulse sequences are equally sensitive to small changes in CBF and CBV, the major concern being that, due to the uniform vascular weighting, GE will lack sensitivity to microvascular tracer transit because of contrast arising from larger veins with a slow flow. This is particularly important in the setting of acute stroke, where MTT is widely used as a predictor of "tissue at risk" after an acute stroke. We addressed this by studying the relationship between relative CBF and CBV values obtained by SE and GE EPI in states of altered flow in a porcine hypo- and hypercapnia model. Furthermore, we addressed the possibility of introducing a conversion factor, previously determined for SE EPI, for determining absolute CBF and CBV by GE EPI perfusion-weighted imaging.

THEORY

MRI CBF Measurements

CBF was measured by MR imaging of nondiffusible tracers as described in detail elsewhere (5,6). In brief,

the concentration $C_{VOI}(t)$ of an intravascular contrast agent within a given volume of interest (VOI) can be expressed as:

$$C_{VOI}(t) = F \cdot \int_0^t C_a(\tau)R(t-\tau)d\tau \qquad (1)$$

where $C_a(t)$ is the arterial input, F is tissue blood flow, and $R(t)$ is the vascular *residue function*, ie, the fraction of tracer present in the vascular bed of the VOI at time t after injection of a unit impulse of tracer in its supply vessel. By treating the residue function as an *unknown* variable, this approach to some extent circumvents the problems of using intravascular tracers for CBF measurements, as pointed out by Lassen (7) and Weisskoff et al (8).

Assuming that tissue and arterial concentrations are measured at equidistant time points t_1, $t_2 = t_1 + \Delta t, \ldots, t_N$, Eq. [1] can be reformulated as a matrix equation:

$$\begin{pmatrix} C_{VOI}(t_1) \\ C_{VOI}(t_2) \\ \cdots \\ C_{VOI}(t_N) \end{pmatrix}$$

$$= CBF \cdot \Delta t \begin{pmatrix} C_a(t_1) & 0 & \cdots & 0 \\ C_a(t_2) & C_a(t_1) & \cdots & 0 \\ \cdots & \cdots & \cdots & \cdots \\ C_a(t_N) & C_a(t_{N-1}) & \cdots & C_a(t_1) \end{pmatrix} \cdot \begin{pmatrix} R(t_1) \\ R(t_2) \\ \cdots \\ R(t_N) \end{pmatrix}$$

$$(2)$$

and solved for CBF $\cdot$ $R(t)$ by algorithms from linear algebra. Østergaard et al (5,6) demonstrated that, by using singular value decomposition (SVD), $R(t)$ and CBF can be determined with good accuracy, independent of the underlying vascular structure and volume, and with raw image signal-to-noise ratios (SNRs) equivalent to those obtainable in current clinical MR imaging protocols.

MRI CBV Measurement

Blood volume was determined by numerically integrating the area under the concentration-time curve during the contrast bolus (defined visually as the range of images during the first pass where the image intensity exceed the noise level) and normalizing it to the injected dose (9):

$$CBV \propto \int_{bolus} C_{VOI}(\tau)d\tau \qquad (3)$$

MATERIALS AND METHODS

Animal Preparation and Experimental Protocol

The project was approved by the Danish National Ethics Committee for Animal Experiments. Ten female country-bred Yorkshire pigs weighing 38–44 kg were used in the experiments. Prior to the experiment, the pigs were housed singly in stalls in a thermostatically controlled (20°C) animal colony with natural lighting conditions. The pigs had free access to water but were deprived of food for 24 hours prior to experiments. Pigs were initially sedated by i.m. injection of 0.25 ml/kg of a mixture of midazolam (2.5 mg/ml) and ketamine HCl (25 mg/ml). A catheter was then placed in an ear vein. After i.v. injection of an additional midazolam/ketamine mixture (0.25 ml/kg), the pigs were intubated and artificially ventilated (Engström Ventilators, Stockholm, Sweden) throughout the experiment, maintaining anesthesia by continuous infusion of 0.5 ml/kg/hr of the midazolam/ketamine mixture and 0.1 mg/kg/hr pancuronium. Indwelling femoral arterial and venous catheters (Avanti size 6–7 F) were surgically inserted.

Throughout the MR experiment, body temperature and expired air CO_2 were monitored (Datex Capnograph, Instrumentarium, Helsinki, Finland). MR imaging was performed in normo- and hypercapnic conditions. Hypercapnia was induced by hypoventilating the pig. Arterial blood samples were withdrawn and analyzed (ABL 300, Radiometer, Copenhagen, Denmark) at regular intervals to monitor blood gases and whole blood acid-base parameters. At the end of the experiments, the anesthetized pigs were sacrificed by i.v. injection of KCl.

MRI Imaging Protocol

Imaging was performed using a General Electric Signa Horizon 1-T imager (GE Medical Systems, Milwaukee, WI, USA). Following a sagittal scout, a T1-weighted three-dimensional (3D) GE sequence (TR/TE 8/1.5 msec, flip angle 20°) was acquired for localizing a suitable slice for perfusion measurements.

For dynamic imaging of bolus passages, GE (TR/TE 500/45 msec, flip angle 20°) and SE (TR/TE 1000/75 msec) single-shot EPI was performed sequentially in random order, each over 2 minutes, starting 30 seconds prior to injection. A period of 30 minutes was inserted between each scan to allow partial washout. In both cases, a 64×64 acquisition matrix was used with a 14×14-cm axial field of view (FOV), leading to an in-plane resolution of 2.2×2.2 mm^2. The slice thickness was 5 mm. A gadodiamide bolus (Omniscan, Nycomed Imaging, Oslo, Norway) of 0.1–0.2 mmol/kg was injected manually at a rate of 10–15 ml/sec, resulting in a bolus duration of less than 1 second. The contrast doses were varied to compare parametric image quality in different contrast doses. The images were normalized to the dose. The choice of dose did not affect conclusions presented here (results not shown). A small predose (0.05 mmol/kg) of gadodiamide was given prior to the dynamic imaging to reduce systematic effects from changes in blood T1.

MRI Image Analysis

We used susceptibility contrast arising from compartmentalization of the contrast agent (2) to determine tissue and arterial tracer levels. We assumed a linear relation between the concentration of paramagnetic contrast agent and the change in transverse relaxation rate ΔR_2, so as to determine tissue and arterial tracer time concentration curves $C(t)$ according to the equation

$$C(t) = k \cdot \Delta R_2(t) = -k \cdot \ln\left(\frac{S(t)}{S(0)}\right)/TE \qquad (4)$$

where $S(0)$ and $S(t)$ are the signal intensities at the baseline and time t, respectively. Note that because of the predose of gadodiamide we assumed T1 to be unaltered during the bolus injection.

The arterial concentration was determined in each animal from 4–6 pixels containing relatively large feeding vessels, typically the middle cerebral artery. The pixels were chosen manually and were believed to cover arteries since they showed an early and large (3–10 times that of gray and white matter) increase in ΔR_2 following contrast injection. Even though these pixels must involve a substantial partial volume effect due to the pixel size relative to the actual size of cerebral vessels, the corresponding concentration-time curve is believed to represent the shape of the arterial input function (AIF) due to the amplitude of the curve. The lack of absolute concentration measurements due to partial volume effect is taken into account by the normalization routine as outlined below. This method has previously been demonstrated to reflect closely actual, arterial levels for the susceptibility contrast agents used in this study, when imaged using SE EPI techniques (10). In Fig. 1, the bolus passage from the AIF from one of the pigs is seen along with bolus passages from regions of interest (ROIs) covering gray matter and white matter in the same pig.

To determine CBF from Eq. [2], the deconvolution was performed over the range of measurements where the arterial input values visually exceeded the noise level (usually about 15 seconds). There were no systematic differences in bolus duration among GE and SE measurements. The integrated area of the AIF was normalized to the injected contrast dose in all experiments, to make comparisons within and among animals. Deconvolution followed smoothing of raw image data by a 3 × 3 uniform smoothing kernel. The height of the deconvolved response curve was considered to be proportional to CBF. CBV was determined by numerically integrating the concentration-time curve from bolus arrival to tracer recirculation.

Throughout the text, when the terms "CBF" and "CBV" are used, we refer to the concepts, bearing in mind that their units, by their derivation from relaxation rate changes, are not those of traditional absolute measurements (ml/ml/min or ml/ml, respectively).

Comparison of MR Images

Pixel maps of CBF and CBV were compared by choosing 12 ROIs, 6 in the gray matter and 6 in the white matter. The ROIs contained 13 pixels on average. ROIs were drawn for each pig, the same ROIs were applied on the GE CBF and the SE CBF map for the same pig, and the values were compared by linear regression. The same procedure was applied for the CBV maps using the same ROIs. Linear regression analysis was performed in each pig to determine the presence of a linear relation between the values obtained by GE and SE. Since GE and SE measurements were performed in both normo- and hypercapnic conditions for each pig, 20 CBF (GE)/
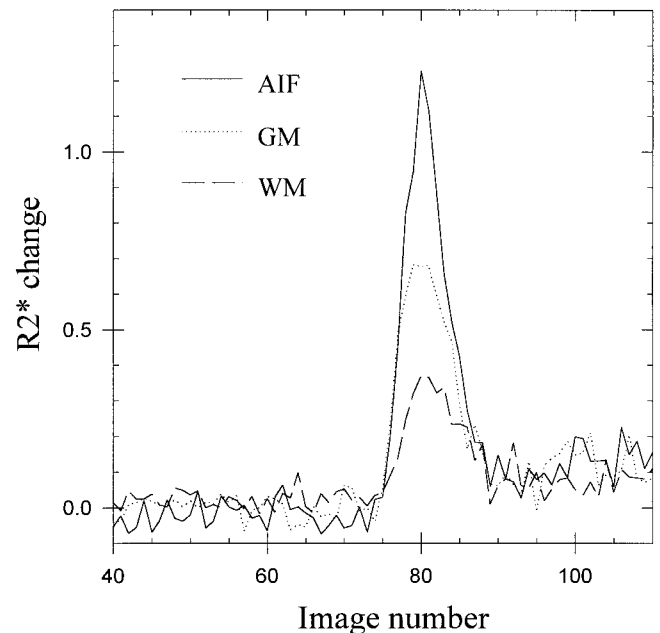
Figure 1. The relative signal intensity for the arterial input function (AIF), a bolus passage from one of the ROIs covering gray matter (GM), and one covering white matter (WM) is shown as a function of image number. The bolus passage is from the GE experiment in pig number 2 with the pig in the hypercapnic situation. Note that the time between each image is 0.5 seconds, since TR is 500 msec in the GE experiment.

CBF (SE) ratios and 20 CBV (GE)/CBV (SE) ratios were obtained. Finally, to test whether a common conversion factor exists between the two measurements, individual slopes were compared by an F-test.

RESULTS

CBF, CBV, and MTT Comparisons by GE and SE

The GE results (CBF and CBV) were plotted as a function of the SE results (CBF and CBV respectively) for both the normo- and hypercapnic conditions. CBF data from one of the pigs appear in Fig. 2. Four linear correlations were calculated for each pig; two for CBF data (normo- and hypercapnia) and two for CBV (normo- and hypercapnia). Table 1 shows CBF and CBV ratios in normocapnic conditions.Table 2 shows the same relations under hypercapnic conditions.No difference was found between the high-flow (hypercapnic) and the low-flow (hypocapnic) situations. Figure 3 shows SE and GE CBF maps for the hypercapnic situation in one of the pigs.

The average value of the slopes for the 20 CBV measurements was 2.96 ± 0.52 (SD). The average value of the slopes for the corresponding 20 CBF measurements was 2.53 ± 0.44 (SD). There was no significant difference in slopes between the pigs for either the CBF ($F_{(19,10)} = 0.64$) or the CBV measurements ($F_{(19,10)} = 0.74$).

Assuming that the GE acquisition reflects total CBV, our findings indicate that SE is sensitive to 34% (1/2.96) of the vasculature.

Since MTT is defined as CBV/CBF, the average rela-
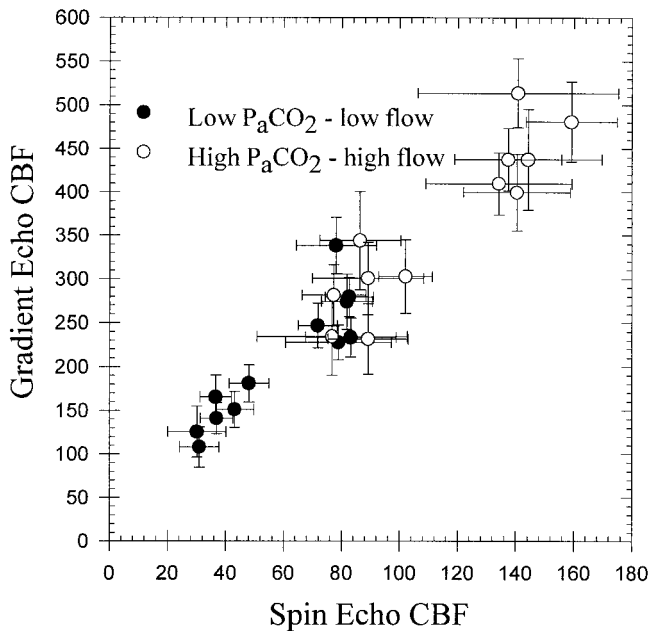
Figure 2. CBF data from pig number 3. GE CBF is plotted along the y-axis and SE CBF along the x-axis. Both normocapnic (black dots) and hypercapnic (open dots) data are presented. Note the close linear relationship.

tionship between MTT measured with GE and SE respectively, can be calculated as:

$$\frac{MTT(GE)}{MTT(SE)} = \frac{CBV(GE)/CBF(GE)}{CBV(SE)/CBF(SE)}$$

$$= \frac{CBV(GE)}{CBV(SE)} \cdot \frac{CBF(SE)}{CBF(GE)} = 2.96 \cdot 1/2.53 = 1.17$$

DISCUSSION

We found a linear relation between relative CBF and CBV values obtained by GE and SE EPI, indicating that GE can detect differences in resting CBF and CBV to the same extent as SE. Furthermore, the slopes of the GE/SE CBF and CBV relations were similar in normo- and hypercapnia, which shows that GE and SE have identical sensitivities for determining flow and volume

Table 1
CBF (GE)/CBF (SE) and CBV (GE)/CBV (SE) Ratios for the Ten Pigs Under Normocapnic Conditions

Pig no.	CBF (GE)/ CBF (SE)	St. error	CBV (GE)/ CBV (SE)	St. error
1	2.47	0.47	3.98	0.57
2	2.02	0.67	3.00	0.98
3	2.87	0.43	2.57	0.39
4	2.04	0.40	2.80	0.61
5	2.98	0.47	3.78	0.46
6	3.17	0.61	2.92	0.26
7	2.91	0.23	3.86	0.40
8	2.59	0.44	2.56	0.44
9	2.41	0.54	3.45	0.67
10	1.99	0.83	3.07	0.94

Table 2
CBF (GE)/CBF (SE) and CBV (GE)/CBV (SE) Ratios for the Ten Pigs Under Hypercapnic Conditions

Pig no.	CBF (GE)/ CBF (SE)	St. error	CBV (GE)/ CBV (SE)	St. error
1	2.07	0.65	2.71	0.85
2	1.68	0.66	2.10	0.61
3	2.85	0.40	2.64	0.37
4	2.70	0.46	2.18	0.42
5	2.74	0.50	2.61	0.34
6	2.18	0.35	2.86	0.22
7	2.63	0.39	3.38	0.38
8	3.38	0.72	2.85	0.55
9	2.68	0.50	2.66	0.47
10	2.32	0.66	3.15	0.93

changes. Our findings agree with those of Mandeville et al [11], who found that SE and GE are equally sensitive to changes in CBV with different levels of CO_2 in the blood. Whether GE and SE have similar sensitivities over an even greater range of flow values, as can occur in disease, remains to be shown.

Our results show that sensitivity to physiologic changes is similar in the two techniques, even though contrast is believed to be generated in vascular volumes with different morphologic characteristics [1,2]. As mentioned above (see Results), the CBV measurements using SE EPI were sensitive to roughly 34% of the vasculature, given that GE is sensitive to the entire vascular bed. This occurred because the GE CBV measurements are on average a factor 2.96 larger than the SE CBV measurements. These results yield experimental support for the microvascular weighting of the SE EPI sequence [1,2] and agree with a report in which the SE EPI sequence was compared with total CBV measured by positron emission tomography (PET) [12]. More importantly, we found that this fraction did not change when hypercapnia was induced, indicating that micro- and total vascular volume changed to the same extent. The fact that the microvascular fraction is unaltered in response to hypercapnia may speak against the notion that vascular volume increase is accounted for by opening of otherwise closed capillaries ("recruitment"). On the basis of large increases in microvascular CBV in hypercapnia, Shockley and LaManna [13] argued that recruitment plays an important role in cerebrovascular regulation. However, the observed microvascular volume increase may be accounted for by dilatation of microvessels: a study by Duelli and Kuschinsky [14] demonstrates that the rat cerebral capillaries dilated significantly, from 4.29 to 5.91 μm in diameter when $PaCO_2$ rose from 21.6 to 95.6 mmHg. This corresponds to an increase in volume of the capillaries of $[(5.91/2)^2 - (4.29/2)^2]/(4.29/2)^2 = 90\%$. The lack of recruitment is also in good agreement with earlier findings [15].

Altering arterial CO^2 levels is widely used as a physiologic challenge to study change in flow and volume. Our study indicates that the increase in CBV occurs to the same extent in micro- and macrovessels.

The MTT values derived by GE EPI were slightly (but not significantly) higher than those obtained by SE EPI. This small difference could be explained by uncertain-
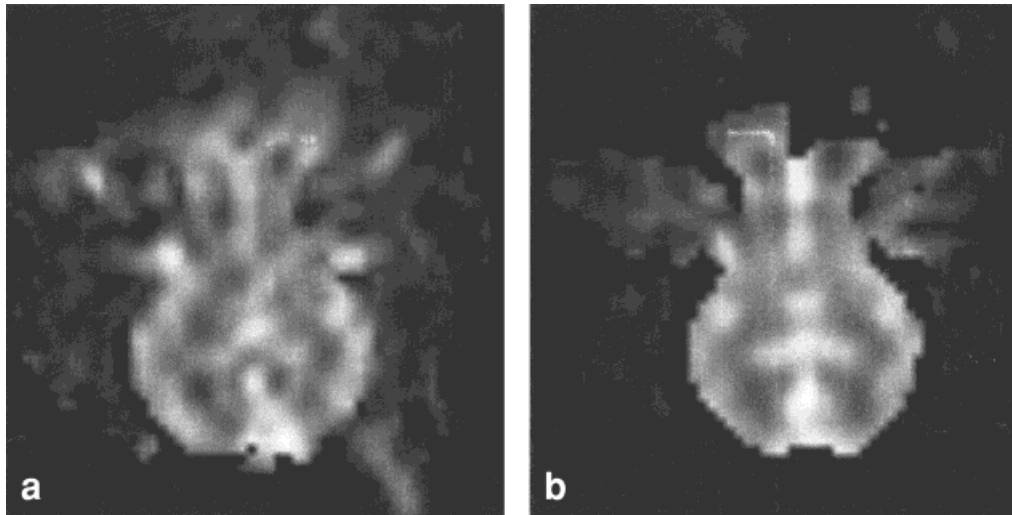
Figure 3. These two images represent CBF maps from the hypercapnic situation in pig number 3, ie, the same pig as in Fig. 2. **a:** The CBF map found with SE. **b:** The map found with GE.

ties in our CBV and CBF measurements, but it could also be explained as a consequence of the sensitivity of GE EPI to larger vessels. The GE sequence is sensitive to the plasma tracer as it passes through venular and venous compartments of the vasculature. The transit time would therefore be longer than when measured by SE EPI, for which sensitivity decreases sharply after tracer has left the capillary compartment. Our results indicate that extra venous passage picked up by GE EPI is short, and when regarding measurements in, eg, acute stroke, the MTT derived by a GE EPI sequence is likely to be as sensitive as the one derived by SE EPI.

A previous PET study (12) has shown that absolute CBF can be calculated from SE EPI data. The conversion factor relating relative CBF found by SE EPI to absolute CBF is, according to that study, 1.09 in the porcine brain. The same constant applies for CBV. Since this study has shown a linear relation between CBF obtained with GE and SE, GE EPI may be used to find absolute CBF values. The constant relating relative CBF found by GE EPI to absolute CBF (absCBF) can then be found as follows:

$$absCBF = 1.09 \times SE\ CBF$$

and

$$GE\ CBF/SE\ CBF = 2.53 \Rightarrow absCBF$$

$$= 1.09/2.53\ GE\ CBF$$

Thus, the conversion factor relating GE CBF to absCBF is 0.43. A similar relation holds for GE CBV.

The experiment was performed at 1.0 T, but generally the T2 and T2* relaxivity of contrast agents scale linearly with field strength (16). The ratios of spin- and gradient echoes are therefore identical at 1.5 T and at higher field strengths.

We used the pig as an experimental animal due to its relatively large brain and the relative ease of handling.

More importantly, previous studies (17) have shown that CBF, CBV, and the cerebral metabolic rate of glucose and oxygen are similar to human values, making it appropriate for studying the physiology of hypercapnia, for example. In the pigs we performed experiments on, we found the major difference from humans in terms of quantifying tissue contrast levels to be a systematically lower hematocrit [0.29 vs. 0.42 in humans (18)], so that conversion to absolute flow values may require different conversion factors (12,19).

CONCLUSIONS

This study demonstrates the following four points: a) although GE is sensitive to the entire vascular bed, it detects the same (small) differences as SE in CBF and CBV; b) SE is sensitive to about one-third of the entire vasculature; c) no sign of recruitment was detected when CBF rose as a result of hypercapnia; and d) CBF found by GE differs from absolute CBF only by a proportionality factor.

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