Improvement in Breast Lesion Characterization With Dynamic Contrast-Enhanced MRI Using Pharmacokinetic Modeling and Bookend $T_1$ Measurements

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Dynamic contrast-enhanced breast MR imaging was performed on 14 patients (five cancerous lesions, nine benign) with slice-selective spoiled gradient-recalled echo (2D SPGR) imaging. Adiabatic saturation recovery $T_1$ measurements were performed before ($T_{1\text{pre}}$) and after ($T_{1\text{post}}$) 2D SPGR imaging. These two “bookend” $T_1$ measurements were used to calibrate the equations which were employed to convert the time course of the 2D SPGR signal strength to $T_1$-vs.-time, which in turn was used to compute the gadolinium concentration-vs.-time ([C](t)) for the lesion. The extraction-flow product (EF) was computed for each lesion by pharmacokinetic modeling of [C](t). For this study, EF provided a sensitivity and specificity for cancer of 100% and 78%, respectively. When only $T_{1\text{pre}}$ was used to estimate [C](t) (which assumes a priori knowledge of the shape and amplitude of the slice profile), the sensitivity and specificity fell to 80% and 56%, respectively. This is presumably due to unexpected variations in the shape and/or amplitude of the slice profile, which could be caused by factors such as patient-to-patient variations in breast geometry or inconsistently set transmit gains. Therefore, both $T_{1\text{pre}}$ and $T_{1\text{post}}$ measurements are necessary for optimum sensitivity and specificity using pharmacokinetic analysis.


Key words: magnetic resonance imaging (MRI); breast cancer; gadolinium contrast agent

Quantitative $T_1$-weighted dynamic contrast-enhanced MRI ($T_1$-w DCE-MRI) is used by many researchers for detecting and evaluating breast disease (1–6). This technique involves intravenous injection of a gadolinium (Gd) contrast agent during rapid (≤ sec), repeated $T_1$-weighted imaging. From these images, the Gd concentration-vs.-time ([C](t)) of a lesion of interest can be estimated (1–4,6,7). Pharmacokinetic modeling can then be applied to [C](t) to extract parameters such as the extraction-flow product (EF), which is equivalent to $K^{\text{trans}}$ (1,4,5,8). These parameters are useful for lesion diagnosis and tracking of treatment progress.

A broad class of pulse sequences frequently used for $T_1$-w DCE-MRI is slice-selective (i.e., two-dimensional) spoiled gradient-recalled echo (2D SPGR) imaging (2,3,6,7,9,10). Such pulse sequences are often used for $T_1$-w DCE-MRI because they provide relatively artifact-free images with the high temporal resolution (<15 sec), which is useful for differentiating benign from malignant breast lesions (11).

The signal-vs.-time (S(t)) of a pixel or region of interest (ROI) in a lesion can be measured directly from the 2D SPGR images. The goal is then to convert S(t) to $T_1$ before injection of the Gd contrast agent ($T_{1\text{pre}}$) or by measuring one or more values of S obtained with special flip angles and TR settings (4,6,7,9,13).

Unfortunately, the 2D SPGR signal strength is very sensitive to even modest variations in the transmit magnetic field ($B_1$), which can cause the signal strength equation to become more and more inaccurate as the $T_1$ shortens (and [C] increases) postinjection (7). This can lead to significant errors (>50%) in the estimated [C](t) (7). Inaccuracies in [C](t) are undesirable because they lead to errors in the estimated pharmacokinetic parameters, reducing sensitivity and specificity and making the method less consistent for tracking treatment progress.

We have demonstrated that a second measurement of $T_1$ (denoted $T_{1\text{post}}$), performed after the dynamic contrast-enhanced 2D SPGR imaging, can minimize the errors in the estimated $T_1$ (7). This second $T_1$ measurement is an important part of the “Bookend Method” that we have developed, which allows $T_1$ to be estimated accurately (<10% error) from 2D SPGR image data, even in the presence of variations in $B_1$ or the slice-select profile shape (7). For the Bookend Method, $T_{1\text{pre}}$ and $T_{1\text{post}}$ are employed to calibrate and correct the 2D SPGR signal strength equation used to estimate $T_1$.

The purpose of this work was to validate the clinical usefulness of the Bookend Method for quantitative $T_1$-w DCE-MRI of the breast. In order to do this, it was first necessary to develop a reasonably fast (~min) clinical $T_1$ measurement imaging pulse sequence which would be insensitive to variations in $B_1$. The Bookend Method was then performed on a group of 14 patients (five cancerous lesions, nine benign lesions). For each lesion, EF was calculated from the estimated [C](t) data and compared to pathological diagnosis. In order to compare the Bookend Method with a more conventional approach of estimating [C](t), the entire analysis was repeated using $T_{1\text{pre}}$ but ignoring $T_{1\text{post}}$.

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MATERIALS AND METHODS

This study was approved by the Kingston General Hospital and Ottawa Hospital Human Research Ethics Boards. Fourteen patients with either palpable lumps or mammographically or sonographically suspicious lesions were recruited who were scheduled for surgical biopsy. Informed written consent was obtained from each patient prior to each MR imaging exam. Imaging was performed with 1.5 T Signa Imaging Systems (General Electric, Milwaukee, WI) and a transmit/receive breast coil (MRI Devices, Milwaukee, WI).

For each patient, the lesion was first localized with conventional MRI pulse sequences (20). Subsequently, the following protocol was used:

1. (T1pre measurement) adiabatic saturation recovery (ASR) 8 slices, recovery times (τ) = 230, 635, 1329, then 2920 ms. This T1 measurement technique is described in more detail below. The total imaging time for this step was ~10 min. For this and subsequent pulse sequences, coronal 5-mm-thick contiguous slices, 256 × 128 matrix size, and 16 cm FOV were used.

2. (2D SPGR imaging) T1-weighted dynamic contrast-enhanced fast spoiled gradient echo (2D FSPGR) TR = 10 ms, TE = 3 ms, flip angle = 20°, 2 NEX, 5–8 slices, temporal resolution = ~12–19 sec, 0.1 mmol/kg Omniscan (Nycomed, Brampton ON, Canada) injected as a bolus after the fourth complete image set (i.e., fourth time point), total duration of dynamic imaging = ~10 min.

3. (T1post measurement) Same as 1 except that the recovery times (τ) were 230, 432, 775, then 2920 ms.

Postprocessing was performed off-line with Matlab (MathWorks, Natick MA). For each 2D SPGR imaging slice which contained part of the lesion, an ROI was manually drawn on the area of the lesion which demonstrated the greatest signal enhancement, defined as ΔS = S(t=2 min) – S(t=0 min). Each ROI covered a group of contiguous pixels for which ΔS was at least 80% of the maximum ΔS for that slice.

Each ROI was propagated through the saturation recovery and 2D SPGR images. T1pre and T1post were each determined with a three-parameter fit to the four recovery points. For each ROI, T1 was calculated from S(t) using the Bookend Method analysis (Method 4 in Ref. 7). For this analysis, T1pre and T1post were used to correct a lookup table that relates S and T1 (7). The change in 1/T1 as a function of time was converted to [C(t)] by dividing by 4.5 mM·s−1 (12). The conversion of T1 to [C(t)] assumed that the intravascular component was insignificant and that there was slow exchange of water between the plasma and the extravascular space (14). Under these assumptions, [C(t)] represents the time course of the average concentration of Gd in the extravascular space (14). The [C(t)] data were fit to a well-known pharmacokinetic model:

\[
\frac{d[C(t)]}{dt} = \text{EF} \left[ C_a(t) - \frac{[C(t)]}{v} \right]. \tag{1}
\]

For this equation, C_a(t) is the arterial input function (AIF), defined as the concentration-vs.-time of Gd in the plasma of the arterial blood supply. For this study, C_a(t) was not measured for each patient. Instead, an approximate average of published data was used (15,16). The peak amplitude (2.7 mM) of the initial bolus phase (t = 0 to ~25 s) of this average AIF was calculated by averaging the peak amplitudes of the six AIF measurements shown in fig. 6 of Fritz-Hansen et al. (15). The initial, rapid washout of the average AIF from that peak value (t = ~25 to 50 sec) was modeled as a simple monoexponential decay with no recirculation. The rate constant for this decay (0.12 s−1) was calculated by fitting a monoexponential decay to the initial washout phase of each of the Fritz-Hansen curves, then averaging the resultant rate constants. The longer, slower washout phase of the average AIF (t = ~50–600 sec) was calculated similarly from data published by Weinmann et al. (16).

The unitless quantity v, a free-floating parameter for the curve fit of Eq. 1, is the volume fraction of extravascular space occupied by the extracellular interstitial space (i.e., the space outside the cells and capillaries). The term EF (the other free-floating parameter) is known as the extraction-flow product. EF was expressed in units of ml/min 100 g, under the assumption of unit density of tissue, to facilitate comparison to other studies (4,5,8). To further facilitate such comparison, the value of EF extracted from the curve fit was subsequently divided by one minus the hematocrit (Hc = 40% assumed). This adjustment made the EF values more consistent with those of many other investigators who use whole blood concentrations for C_a(t) instead of plasma concentrations (4).

For each lesion, a set of EF values was therefore obtained which corresponded to the set of ROIs which had been drawn. The maximum EF value in that set was defined as the one which was representative of the lesion. As a comparison, the entire analysis was repeated using the ROI which corresponded to that maximum EF value, this time assuming that there were no imperfections in the 2D SPGR signal strength equation (e.g., no variations in Bi or slice profile shape). Under this assumption, [C(t)] could be estimated accurately using only the T1pre measurement (4,7,13). This alternative analysis method is known as the “Single-T1pre Method” (Method 2 in Ref. 7), in contrast to the Bookend Method, which utilizes both T1pre and T1post.

The T1pre and T1post measurements were obtained with an ASR pulse sequence. For the acquisition of each line of k-space, a nonselective sin/cos adiabatic saturation pulse was applied, followed by a recovery time τ, followed by readout pulses and data acquisition for all slices (17). An adiabatic saturation pulse was used in order to make the T1 measurement less sensitive to Bi inhomogeneities. The nonselective sin/cos pulse was applied for 102 ms. This pulse started 233 Hz off-resonance and ended with a maximum Bi amplitude of ~0.073 Gauss. The pulse sequence had conventional, sequential phase encode ordering and interleaved slice ordering. Thus, after the recovery time τ, slices 1, 3, 5, then 7 were read out, followed immediately by slices 2, 4, 6, then 8. The pulse sequence was repeated with the same τ until an entire image had been acquired. One image was acquired for each of four values of τ as described above.

The peak specific absorption rate (SAR) generated in the breast by the ASR pulse sequence was calculated to be under 8 W/kg, which is the limit recommended by the
United States Food and Drug Administration for a local transmitter coil. This calculation was done using manufacturer-supplied information and was based on the assumption that the transmit/receive breast coil and the transmit/receive head coil behave similarly in terms of RF heating.

Numerical simulations were performed in order to determine the theoretical accuracy of this ASR $T_1$ measurement technique. $T_1$ was fit to simulated, noiseless, recovery data for $T_1$ values of 230, 470, 877, and 3000 ms. Recovery data were generated for all combinations of the following parameters: $T_1$ (400, 1200 ms); $T_2$ (50, 300 ms); $B_1$ inhomogeneity (i.e., the actual $B_1$ divided by the expected $B_1$) (0.5, 0.75, 1.0, 1.25, 2.0); and resonant offset ($-25$, $0$, 25 Hz). For each case of $T_1$, $T_2$, $B_1$ inhomogeneity, and resonant offset, the effect of the adiabatic pulse was calculated by solving the Bloch equations numerically. The readout pulses were assumed to be single-lobed sinc pulses which are typically used in 2D SPGR imaging.

Phantom experiments were also performed to test the accuracy of the ASR technique: 12 mm- and 5 mm-wide plastic tube phantoms were filled with different aqueous concentrations of Gd contrast agent providing $T_1$ ranging from $1290 \pm 10$ ms down to $450 \pm 5$ ms as measured by inversion recovery (IR). This range of $T_1$ was used because it is approximately the range expected in vivo. The IR measurements were performed with a single-slice IR technique with 12 inversion time (TI) values ranging from 50–8000 ms, and TR = TI + 9000 ms. For this work, the IR measurements were considered the “Gold Standard” measurements of $T_1$.

For ASR imaging, the tubes were placed upright at 8 to 9 different positions in a 9-cm high plastic container of water. The transmit/receive breast coil was used to obtain coronal images of this container with a slice thickness of 5 mm, 8 contiguous slices, matrix = $256 \times 128$, and field of view = 16 cm. $T_1$ measurements with ASR were repeated six times for different locations in the water container and different arrangements of the phantom tubes. A total of 816 ASR $T_1$ measurements were performed, covering a volume of 830 cm$^3$, which is nearly all the useful imaging volume of the coil. $\tau$ values of 230, 635, 1329, and 2920 ms were used to measure the $T_1$ of the tubes with $T_1 > 650$ ms, while $\tau$ values of 230, 432, 775, and 2920 ms were used to measure the $T_1$ of the tubes with $T_1 < 650$ ms. These sampling schemes were the same as those which were used for the patients to measure $T_{1\text{pre}}$ (which was expected to be >650 ms) and $T_{1\text{post}}$ (which was expected to be <650 ms).

RESULTS

For the simulations, the ASR technique maintained reasonably small errors (<10%) even down to $B_1$ inhomogeneities of 0.5. In phantoms, the ASR technique measured $T_1$ accurately (5%) for all experiments. Figure 1 shows representative ASR and 2D SPGR images. Figure 2 shows the correction that had to be applied to the 2D SPGR signal strength equation for the Bookend Method, as a function of $1/T_1$ for all 14 patients. The ordinate may also be described as the ratio of the actual 2D SPGR signal strength to the theoretical 2D SPGR signal strength.
FIG. 3. The concentration of Gd in tissue as a function of time ([C](t)) for two different lesions (benign proliferative dysplasia and infiltrating moderately differentiated ductal carcinoma). The solid and dotted lines show the curve fits for the pharmacokinetic model: a: [C](t) calculated with the Single-\(T_1\)pre Method. For this data, the EF of the benign lesion was 44.4, compared to 26.8 for the cancerous lesion. b: [C](t) calculated with the Bookend Method. This time, the EF of the cancerous lesion was much higher than that of the benign lesion (EF = 43.1 compared to 9.8).

DISCUSSION

The results of this study show that a single preinjection \(T_1\) measurement is not sufficient for estimating [C](t) reliably from rapid 2D SPGR imaging for pharmacokinetic modeling. This is because the discrepancy between the measured 2D SPGR signal strength and its theoretical value is not consistent from lesion to lesion (Fig. 2). This inconsistency is presumably due to unexpected variations in the \(B_1\) or slice-select profile, which could be caused by factors such as patient-to-patient variations in breast geometry or inconsistently set transmit gains. The Bookend Method, however, circumvents these problems by obtaining a case-by-case empirical calibration of 2D SPGR signal strength vs. \(T_1\). The [C](t) as estimated by the Bookend Method should therefore be much more accurate than [C](t) estimated by the Single-\(T_1\)pre Method. This is consistent with the fact that the Bookend Method provided higher sensitivity and specificity for this study than the Single-\(T_1\)pre Method, given the assumption that there should be a significant separation in EF values between cancerous and benign lesions.

For the Bookend Method, it is important that the accuracy of the \(T_{1\text{pre}}\) and \(T_{1\text{post}}\) measurements not be adversely affected by the same variations in the \(B_1\) or slice-select profile which render the Single-\(T_1\)pre Method unreliable. For this reason, we chose a \(T_1\) measurement method (ASR) which would be relatively unaffected by \(B_1\) inhomogeneities. The ASR method demonstrated low systematic errors (<5%) for both the simulations and phantom experiments.

The principal drawback of the Bookend Method is that the exam time must be lengthened to accommodate the \(T_{1\text{post}}\) measurement. If limiting the total exam time is crucial, both bookend \(T_1\) measurements could be performed with a faster, more efficient method such as one of the Look-Locker techniques (18). Whatever fast \(T_1\) measurement method is chosen, it must maintain the same spatial resolution as the 2D

56%, respectively. For the Bookend Method, the sensitivity and specificity were 100% and 78%, respectively.
SPGR imaging and not suffer problems from \( B_1 \) inhomogeneities or multislice interference. One of the weaknesses of this study, and most other studies which have been published on breast MR, is the lack of a true arterial input function (19). The assumed input function used was based on the approximate average of some input function data obtained from a small group of subjects (15,16). However, changes in the input function from one individual to another could cause significant changes in the \( [C(t)] \) data, leading to unwanted variations in the measured pharmacokinetic parameters (19). Based on the work by Port et al. (fig. 7 of Ref. 19), it can be estimated that using the same input function for all patients will cause unwanted errors in the pharmacokinetic parameters of about 25% on average. However, a certain fraction of patients (~15% in Port et al.) will have input functions that deviate very significantly from the average, leading to very large (>40%) errors. Therefore, there is a need to develop rapid, accurate methods for measuring the arterial input function while simultaneously acquiring the \( \text{Gd concentration}-\text{vs.}-\text{time} \) in the breast tissue \( ([C(t)]) \).

**CONCLUSIONS**

For dynamic contrast-enhanced MR imaging of the breast, when estimating \( [C(t)] \) for a lesion from \( T_1 \)-weighted 2D SPGR imaging, it is not sufficient to use a single preinjection \( T_1 \) measurement \( T_{1\text{pre}} \) to calibrate the signal strength equations used to convert signal strength to \( T_1 \). This is because the discrepancy between the measured signal strength and its theoretical value is not consistent from lesion to lesion. A second \( T_1 \) measurement, performed after the dynamic contrast-enhanced imaging \( T_{1\text{post}} \), must be done to obtain a case-by-case empirical calibration of signal strength vs. \( T_1 \). This improves the accuracy of the estimated \( [C(t)] \) and ultimately improves sensitivity and specificity for the pharmacokinetic parameter(s) used to differentiate benign from malignant tumors (e.g., the extraction-flow product which was used in this work). For this particular patient study (\( n = 14 \)), using the two \( T_1 \) measurements (the “Bookend Method”), gave a sensitivity and specificity of 100% and 78%, respectively, compared to use of the preinjection \( T_1 \) measurement alone, which had a poorer performance (80% and 56%, respectively). The power of the Bookend Method is that, as long as \( T_{1\text{pre}} \) and \( T_{1\text{post}} \) are measured accurately, \( [C(t)] \) can be estimated reliably from 2D SPGR signal strengths without any a priori knowledge of system imperfections.

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