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13. Abstract ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*

This research project focused on the development of MRI arterial spin tagging to non-invasively measure breast tissue perfusion. The specific aims were to (1) refine arterial spin tagging pulse sequences, (2) develop automated data analysis software, and (3) compare the technique to first-pass contrast-enhanced MRI and biopsy. New spin-tagging pulse sequences were developed for the GE 1.5T Advantage and Horizon LX CV/I MRI systems, and new image processing software, including software for statistical analysis of spin tagging and contrast enhanced dynamic scans, were written for use in the clinical setting. Year three and no-cost extension years of the project focused on clinical comparison of arterial spin tagging with first-pass, contrast-enhanced MRI in patients with unbiopsied breast masses, for aim (3). Studies showed that the new techniques were capable of locating regions of the breast with enhanced capillary flow, and that in patients these regions correlated well with malignant tumor location. The analysis software enabled easy and consistent visualization of spatial and temporal signal changes in the breast tissue, and analysis could be done by someone without computer expertise. The number of clinical studies completed was not sufficient for statistical results to be conclusive.

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(4) INTRODUCTION

This research project concerns the development of MRI arterial spin tagging to non-invasively measure breast tissue perfusion. MR dynamic first-pass contrast-enhanced imaging has shown that malignant and benign breast lesions can be distinguished. However, it may have limited importance in clinical breast diagnosis due to significant false-negatives and false-positives. The arterial spin tagging technique was developed to measure tissue perfusion parameters without the use of contrast, and has been successfully demonstrated in brain and kidney. The specific aims are to (1) refine arterial spin tagging pulse sequences and imaging protocols, (2) develop automated data analysis software for measurement of breast tissue parameters, and (3) compare the technique to first-pass contrast-enhanced MRI and biopsy. We will test the hypothesis that arterial spin tagging provides accurate and precise discrimination between normal tissue, benign and malignant lesions, when differences in perfusion and T_1 exist. Lesions will have been previously detected by clinically accepted diagnostic imaging procedures, and by biopsy. Statistical analysis will be performed to access the correspondence between arterial spin-tagging and biopsy, and to establish the relative value of spin tagging compared to first-pass contrast-enhanced MRI. We hope to establish that, relative to using first-pass contrast-enhanced imaging, false positives and negatives are reduced using arterial spin tagging by virtue of increased image signal-to-noise ratio (SNR), higher spatial resolution, and the unique ability to obtain estimates of macromolecular bound fluid fractions. The scope of effort on the project is mainly limited to the technical aspects of development of a new methodology. However, the project also includes a performance comparison with the current gold-standard methodology. The technique will be evaluated in sixty patients, with roughly equal numbers of benign and malignant lesions.

(5) BODY

Chronological overview

This section details the experimental methods, results and discussion in relation to the Statement of Work outlined in the proposal. The first subsection provides brief paragraphs of the accomplishments. Detailed discussion of these accomplishments is provided in the second subsection.

There were two main contributions of the work during the first year of the project. The first was the discovery of a multitude of unrecognized sources of T_1 estimate errors, the recognition of the profound sensitivity of perfusion measurements to T_1 estimate errors, and the development of robust pulse sequences and analysis methods to derive accurate T_1 estimates with inherently noisy and confounded signal data. The second was the development of the software program, BrView, to allow rapid review, quantitative analysis, and assessment of the multitude of different breast images and timeseries data that is obtained in each patient study.

During the later part of 1998 and throughout 1999, the project was delayed. The major deficiency in progress was in the third technical objective. Specifically, a comparison of the arterial spin tagging sequence with the dynamic contrast enhanced first pass study had not been achieved. Roughly 60 patients should have been scanned by late 1999 in the project, but only two had been scanned. The deficiency in progress was due to problems in finding a replacement physician for the co-I on the project, Rebecca Zulim, who left UC Davis Medical Center November 1, 1998. Also, UCD Medical Center Radiology Department upgraded all their MRI

systems from Signa Advantage MRI systems running the Genesis 5.x operating system, to Signa CV/I MRI systems running the LX 8.2.5 operating system, resulting in several months during which the new pulse sequences were not compatible with any of the MRI systems we had access to. Substantial time was needed to convert the pulse sequences to the LX 8.2.5 operating system (platform) from the Genesis 5.x platform. This time period for upgrading the UCD Med Center MRI systems was not planned in advance, and the time to convert our research software was not written into the approved Work Statement. I along with the graduate student on the project, David Zhu, worked on the conversion of the arterial spin tagging pulse sequences, and on the development of new arterial spin tagging sequences based on our "odd-hybrid" EPI technique, which was published in 1999 (See References). Also, advances were made in our image processing software for the project. Because of the delays, the budget and schedule was officially pushed back 6 months, into the 3rd year which had a light work schedule. For full details, please see the referenced letter dated April 22, 1999, and the approved Budget change, in the Appendix of the 1999 Report. The project continued into the 3rd year, as specified by an approved revised schedule and budget. Dr. PD Schneider became the co-investigator on the project in early 1999.

In 2000, David Zhu completed his dissertation (attached in Appendix of the 2000 Report) and compiled the software on CD-ROM (enclosed in the 2000 Report). A poster presentation was given at the USAMRMC BCRP meeting in Atlanta (attached in Appendix of the 2000 Report). A comparison of the arterial spin tagging sequence with the dynamic contrast enhanced first pass study intended for year 3 was not completed. Although Dr. Schneider agreed to serve as a collaborator for this period, patient recruitment was ineffective, due I believe to several other breast cancer research protocols which had higher priority for enrolling patients. I had submitted a revised project schedule and budget in May 1999 based upon having Dr. Philip Schneider as a collaborator, and these were approved, but the revisions were not implemented due to the lack of patient recruitment into the study. During the grant year ending Sept. 29, 2000, exactly $12,971 was spent from grant funds, for support of Dr. Zhu during the last three months (Oct 1999 – Dec 1999) of his employment at UC Davis, and 3% PI salary support. No salary support was provided to the co-I. As of Sept 2000, $71,408 (27.2% of total award) remained unexpended.

Between Sept 30, 2000 and Sept 29, 2001, the project remained inactive. No salary support was provided to the principal investigator or co-I, and there were no direct cost expenses. As of Sept 2001, $ 69,719.04 (27% of total award) remained unexpended. In December 2001, I received another extension to attempt to complete the work of the proposal. Unfortunately, the newly created recruitment mechanism did not work well, and also support personnel were not available as had been planned.

During 2002, David Zhu (now at GE Medical Systems) and I finished a manuscript that discusses all of the completed work of this project (39 double-spaced pages – See Appendix). Grant funding was taken to support my efforts in running additional data analyses and co-writing the manuscript. It was submitted to Magnetic Resonance in Medicine Sept 26, 2002, and reviews were returned Nov 14, 2002. The paper received excellent scores from the reviewers and was deemed publishable by the Editor. But, revision is required. The paper and the reviewer's comments are included in the Appendix.

During the grant year ending Sept. 29, 2002, no patient studies were completed due to a lack of effective patient recruitment mechanism, and due to an upgrade of our MRI system from the LX 8.2.5 to the LX 8.4M4 platform, which necessitated rewriting the pulse sequences into 84M4 base code. Also, Mahmoud Abdulhusain, a BME graduate student who was scheduled to have

completed his PhD qualifying examination, and become involved in this project, required an additional six months to prepare for the qualifying examination, and furthermore did not pass the exam when taken March 2002. Mahmoud felt he had could not devote any time to the research project and in fact is preparing for his 2nd examination to be taken March 2003, and unable to contribute. The grant was closed June 30, 2002 with $40,640 unspent (by September 2002 ledger).

Summary of accomplishments in relation to Statement of Work

NOTE: In the paragraphs below, we refer to the specific years of grant funding as 1998, 1999, 2000, 2001, and 2002. The stated year indicates the year ending on Sept. 29 of that year, e.g. an activity that occurred "in 1999", means that the activity occurred between Sept. 30, 1998 and Sept. 29, 1999. Additional details regarding the activity can be found in the 1999 Annual Report.

Technical objective 1

Task 1: Months 1-6: Implementation and testing of magnetization transfer pulses for both arterial tagging and first-pass contrast enhanced sequences.

This task was completed. In the 3rd year (2000) of the grant, magnetization transfer (MT) was fully developed and tested with the EPI-based spin tagging sequence.

In 1999, Magnetization transfer (MT) was first implemented with the EPI-based spin tagging sequence (see Figure 1 of 1999 Report). Due to hardware and compiler problems that were investigated by GE, the pulse sequence was implemented only on the pulse sequence simulation software (EPIC), not on the MRI system.

Testing of MT using the fast SPGR-based sequence revealed that MT would not be effective in this application. Furthermore, because the RF pulse used for MT was long duration (16 ms), the "small TR" (*optr*) period of the fast SPGR sequence was effectively doubled in length. Thus, the scan time was no longer short, and the signal upon which the perfusion measurement was based became more distorted. Because of concerns regarding the ultimate utility of the MT technique, we decided in 1999 that implementation and testing of arterial spin-tagging sequence based on echo planar imaging (EPI) data acquisition should be a higher priority. EPI based spin-tagging technique could theoretically improve the accuracy of the T1 estimation, which we had studied and worked with extensively (see 1999 Report). MT was fully implemented after completion of the EPI sequence.

Task 2: Months 1-9: Implementation and testing of interleaved high-resolution imaging technique, for both arterial tagging and first-pass contrast enhanced sequences.

This task was completed. In 1998, an interleaved arterial spin-tagging technique, that allows high resolution (e.g. 256 x 256 or more) was implemented and tested. We also implemented a rectangular data acquisition technique, which acquired data sets that have different numbers of points along the frequency and phase encode direction. The 256 x 240 interleaved acquisition provided the best spatial versus temporal resolution tradeoff, and was used for our later studies.

When the UC Davis Imaging Center MRI system was upgraded to a CV/I system with the LX 8.2.5 platform in early 1999, we studied the EPIC LX 8.2.5 programming language for pulse sequence development on this new MRI system. The transition to the new research MRI required a complete rewrite of all pulse sequence software that had been developed for this project. In

addition, the pulse sequences were revised to utilize the high performance gradients (40 mT/m peak, 150 mT/m/ms rise) of the system. The other sequences in the breast imaging protocol were set up for the new LX 8.2.5 platform.

The fast SPGR-based arterial spin tagging pulse sequence was converted from the Genesis 5.4 platform to the LX 8.2.5 platform. The converted sequence was also improved to achieve higher resolution with a shorter overall scan time. The new MR system provided higher peak gradient amplitude and slew rate. Fast data acquisition, which required the higher read-out gradient amplitude (4.0 g/cm) could be specified, and consequently the data acquisition period (*optr*) was shortened from 16.62 ms to 12.5 ms. Since *optr* was shortened, a larger matrix in the phase encode direction could be specified. The resolution of 256 × 256 matrix became standard, using one-half phase field of view acquisition. The total time for the image acquisition (the TR period), including the global inversion RF pulse, decreased from 2.7 seconds to 2.22 seconds with these sequence improvements. The performance of this new sequence was confirmed using phantoms and one test subject.

In 1999, the authors developed a new pulse sequence using interleaved EPI sequence (see References) for the Genesis 5.4 platform. In 2000, the EPI-based arterial spin tagging sequence was rewritten for the LX 8.2.5 platform and verified on the research MRI system. The data acquisition scheme was based on our published high-resolution odd-number interleaf EPI sequence (see References). A corresponding algorithm for ghost correction was published later in 2001 (see References).

Using the new CV/I MRI system, the polarity alternation scheme for each successive interleaf, which worked successfully on the older Advantage system, caused the new system to hang. Substantial time was expended understanding the problem. In October 1999, an alternative approach was devised and successfully implemented to eliminate the requirement of polarity alternation. One persistent problem that we had with all interleaved EPI sequences was somewhat reduced SNR relative to theoretical predictions. The cause of this was determined to be due to variation in spatial eddy current causing variable alignment of magnetization phase in each interleaf.

In the final arterial spin tagging sequence using the interleaved EPI acquisition, the following steps are performed at each interleaf: (1) non-selective RF inversion pulse, and (2) 20 EPI acquisitions, each of which is preceded by a 10^0 RF pulse (Figure 2). The 20 acquisitions are played out with a repetition time (*optr* in Figure 2) of 100 ms. Each acquisition defines one point on a T_1 recovery curve. The total time for each interleaf (*TR* in Figure 5.10 of 2000 Annual Report) is 2 seconds. Data for the other interleaves is collected in the same fashion in subsequent TR intervals. Figure 3 of the 2000 Annual Report shows the loop nesting. The completed set of images, showing T1 recovery of the magnetization, is acquired in two seconds times the number of interleaves.

Task 3: Months 1-9: Analysis of spin tagging sequence to understand causes of existing baseline offsets, effects of inversion slice transition profiles, and effects of RF flip angle profile on the measurements, with implementation and testing pulse sequence modifications to minimize these imperfections.

This task was completed. In 1998, matching of inversion and excitation slice profiles was greatly improved by using customized RF pulses designed with the Shinnar-Le Roux (SLR) algorithm (see References in 1998 Report). Also, the data processing technique developed that year (based

on a semi-log linear regression of inversion time (*TI*) dependent signal) significantly reduced the previously reported problem in measuring the longitudinal relaxation time (T_1) caused by baseline offsets, and by the uncertainty in the effective inversion time. The optimal RF flip angle for spin excitation during spatial encoding was found to be 10 degrees, based on experiments over a range of flip angles. The SPGR sequence was formally evaluated for these effects, and optimized. The EPI arterial spin tagging sequence was not formally evaluated for these effects. The solutions found for the SPGR sequence, for the inversion slice transition profiles, and effects of RF flip angle profile, were applied. In years 2000-2002, no new work was necessary for this task.

Technical objective 2

Task 4: Months 3-15: Software for automatic estimation and error analysis of perfusion, tissue water longitudinal relaxation time, and extracellular fluid volume fraction from mathematical models and user-defined ROIs from spin tagging timeseries. Implementation of pharmacokinetic model calculations and error analysis for first-pass contrast enhanced imaging.

This task was completed, except for the implementation of a pharmacokinetic model, which was renamed Task 7. In 1998, a software program (BrView) was written in C, X Window System, and Motif, and implemented on an SGI O2 computer (paid for by grant funds) for analyzing and visualizing the MR images and timeseries. Much effort was expended on developing the capability to easily review all of the images taken in each study, and cross-reference pixel locations on different image types. Much more effort than anticipated was needed to develop a robust technique for identifying so-called "suspicious regions" of cancer, based on the T_1 and perfusion measurements. The accurate measurement of T_1 was critical to the accurate measurement of perfusion, and much effort was given to improving the method of estimating T_1. The final method for T_1 estimation is based on a semi-log linear regression technique developed by the investigators. The T_1, perfusion (f/λ) and standard errors of these quantities are estimated automatically using this robust method. So-called "feature images" display these quantities in color and grayscale. These quantities are used to calculate a "suspicion index" for each pixel, and thereby identify regions of breast tissue suspicious for malignancy.

In 1998, the pharmacokinetic model calculations and error analysis for first-pass contrast enhanced imaging was not completed. However, the software did allow the user to display the time profile of the dynamic signal at any pixel, by clicking on that pixel of the reference image of the dynamic study.

In 1999, image processing software development continued. Improvements in the BreastView program, development of "dispAlls" program for analysis of general MRI images, and implementation of statistical analysis of breast lesions based on Bayesian approach, were completed. Statistical analysis of available breast lesion data continued (See 1999 Annual Report). In 2000 through 2002, no new software related to this task was developed.

Task 5: Months 3-15: Software for registration (including implementation and testing of motion correction and physiological noise reduction algorithms) and overlay of images from high resolution T_1 weighted, spin-tagging, and contrast enhanced studies.

This task was completed. In 1998, several features were included in the BrView software program related to this task. Image pixels containing high values of perfusion (f/λ), and moderate to high values of T_1, and low standard errors, were identified as suspicious for cancer, and

assigned a "suspicion index" based on finding similar abnormal values at spatially adjacent pixels. The program allowed color overlay of "Suspicious pixels" on the high-resolution T_1 and T_2 clinical images, and simultaneously presented the first-pass contrast enhanced timeseries at these pixels. This capability provided the user with a comprehensive anatomical and functional view of the suspicious regions, and facilitated making a decision regarding the malignant nature of the lesion. Finally, a motion estimation and artifact correction algorithm was developed and implemented in a separate software program, with the intent on incorporating it into BrView.

In 1999, the BreastView program was further upgraded and enhanced with the latest algorithms for processing and analysis of breast imaging studies, including those for spin-tagged and dynamic contrast enhanced images. Between October 1998 and April 1999, the BreastView program was made "clinician-friendly". The graphical user interface was improved to guide the user through the entire visualization and analysis process for a breast imaging study. A "Help" button, linked to an extensive set of manual pages, was presented on the first page of the interface. The button was linked to an html file with necessary operating instructions. The help files were written for clinicians. The clinician could now begin using the program without first studying the written instructions. If an inappropriate option was selected, the program provided help to the user to select a more appropriate option. Several new features and functions were implemented, as indicated on Figures 6 and 7 in the 1999 Annual Report. The most important new functions of BreastView concerned analysis of the first-pass contrast enhanced images. The program now created an image based upon the time derivative of the rate of rise of the signal to better visualize the contrast enhancement (See Figures 4 and 5 of 1999 Annual Report).

In 1999, the "dispAlls" program was written for quickly viewing and performing ROI analysis on one or a series of breast images. The program was particularly useful for quickly reviewing the timeseries of signal changes in an ROI from the dynamic contrast enhanced studies. The program displays one image, or a sequence of images. Images with or without an Signa image header can be read. The program performs an ROI analysis and plots the calculated values. In 2000-2002 there were no further enhancements of this program.

Technical objective 3

Task 6: Months 9-24: 60 patients with malignant and benign breast lesions will be imaged using T_1 weighted, first-pass contrast enhanced, and arterial spin tagging MRI pulse sequences.

This task was not completed. At the end of 1998, we had thus far recruited two patients for both first-pass contrast enhanced and arterial spin tagging MRI pulse sequences. In 1999, with software infrastructure for the study substantially done, we began trying to improve the rate at which patients are recruited into the study. Unfortunately, in 1999, no additional subjects were done, due to the loss of Rebecca Zulim, MD as the co-investigator on this study, and also due to the transition to a dedicated research MRI system that operated the LX 8.2.5 platform, as described more thoroughly in the 1999 Report. In years 2000-2002, no additional subjects were done. Significant time was spent setting up various recruitment paths, but these proved to be ineffective. We asked for two one-year no-cost extension to accomplish this task. The documentation for these no-cost extensions is included in the Appendices of the 2001 and 2002 (this) Report.

Through Sept 1998, a total of eighteen subjects, including 11 patients referred by their physicians and seven volunteers, had participated in our breast studies. It is important to emphasize that

only two patients used the specific Human Subjects Protocol developed for this USAMRMC project (DAMD17-97-1-7030). The other 16 subjects were scanned under a different Human Subjects Protocol for general MRI technique development, including 12 of these prior to this USAMRMC project initiation on Sept. 29, 1997. The data from these subjects is presented here as background information. Three patients and two volunteers were eliminated from the analysis because the studies could not be completed, or because image quality was poor due to excess motion, or due to the mass being along the lateral chest wall. There were a total of 13 cases useful for analysis. Analysis was done using the program BreastView. For these cases, the suspicious pixels were identified based on the following criteria: T_{1n}: > 0.5 sec f/λ: > 0.1 sec^{-1}, STD of f/λ: < 0.1 sec^{-1}, and the suspicion level threshold was set at 20.2%. The 1999 Annual Report provides a complete table of results for these subjects and patients. Based on the summary shown in Table 8.5 of that Report, the number of true positive (TP) is 2; the number of false negative (FN) is 0; the number of false positive (FP) is 3 and the number of true negative (TN) is 8. Therefore, the true-positive fraction or sensitivity is 100%, calculated by TP/(TP+FN). The false-positive fraction is 27.3%, calculated as FP/(FP+TN). The specificity is 72.7%, which is equal to one minus the false-positive fraction. Because the number of cases investigated is small, the values do not have sufficient statistical confidence to confirm the usefulness of the technique.

Task 7 (listed as Task 6 in the original grant application): Months 12-36: Automated pharmacokinetic analysis, blinded image reading, and statistical comparison of arterial spin tagging, contrast enhanced MRI, and biopsy results.

This task was partially completed. In 1999, we developed an analysis program for the detection of the features of the dynamic contrast enhanced study, and developed a Bayesian statistical analysis for estimating the malignant status of the lesion. This is described in detail in the 1999 Report. Pharmacokinetic analysis based upon a model of Gd and arterial spin exchange between tissue compartments was not completed.

Detailed description of the accomplishments

Descriptions of Technical Contributions

Our technical contributions to 1. Pulse sequence design, 2. Clinical breast imaging protocols, 3. Perfusion image data analysis, and 4. Image processing of dynamic images, have been summarized in the section above. The 1998 and 1999 Annual Reports, and the Manuscript provided in the Appendix, discusses these contributions in detail.

Results of in-vitro and in-vivo testing

In 1998, the success of the arterial spin tagging pulse sequence in measuring perfusion was first proven by the result of flow phantom studies. All studies showed that there was a linear relationship between f/λ and actual flow. All evaluated flows were within the range of tissue perfusion (Figure 7 of 1998 Report). Furthermore, the T_{1n} values obtained in the non-selective condition, at four different flow rates, were as expected, specifically 1.232 +/- 0.034 sec. A brain imaging study was performed to further evaluate the arterial spin tagging pulse sequence. In 11 different regions of interest (ROIs), defined at several different slice locations, white matter had

T_{1n} equal to 0.495 +/- 0.021 sec, T_{1s} equal to 0.487 +/- 0.022 sec, and f/λ equal to 0.030 +/- 0.075 sec^{-1}, ranging from 0 to 0.131 sec^{-1}. Gray matter in this study had T_{1n} equal to 0.665 +/- 0.065 sec, T_{1s} equal to 0.629 +/- 0.035 sec, and f/λ equal to 0.081 +/- 0.054 sec^{-1}, ranging from 0.037 to 0.170 sec^{-1}. In two normal breast studies, at 14 different ROIs defined at several different locations, parenchyma (glandular tissue) had T_{1n} equal to 0.772 +/- 0.088 sec, T_{1s} equal to 0.709 +/- 0.062 sec, and f/λ equal to 0.109 +/- 0.053 sec^{-1}, ranging from 0.043 to 0.190 sec^{-1}. Normal fat tissue had T_{1n} equal to 0.377 +/- 0.069 sec, T_{1s} equal to 0.363 +/- 0.056 sec, and f/λ equal to 0.086 +/- 0.073 sec^{-1}, ranging from 0.003 to 0.177 sec^{-1}. The values resulting from the head and normal breast studies were within expected ranges.

Results of patient studies

Cases done in 1997-8 are described in detail in the 1998 Annual Report. Analysis was done using the program BrView. In summary, there was partial agreement (2 of 4) between spin tagging and biopsy assessments of malignant disease. However, spin tagging may be able to detect abnormal regions not evaluated by the biopsy. Arterial spin tagging results were convincing when suspicious regions overlapped abnormal regions seen on standard clinical T_1, T_2 and proton-density weighted images. Unfortunately, standard clinical images often did not reveal any abnormal tissue, concurring with the view that standard clinical MRI is not definitive in the assessment of breast lesions. Dynamic first-pass contrast-enhanced imaging is definitely needed to help validate the spin tagging technique. In addition, results from X-ray mammography and ultrasonography will be compared, as has been done for prior studies (see page 40 of 1998 Annual Report).

(6) Key Research Accomplishments

In 1998:

A. Pulse sequences for Version 5.5 of MRI System.

1. Arterial spin tagging pulse sequence based on SPGR.
2. Support of symmetric centric *k* space data acquisition.
3. Optimized RF pulses using SLR algorithm.
4. Odd-number interleaved *k*-space acquisition applied to SPGR

B. New breast imaging protocol for Signa Advantage system.

C. Semi-log curve fitting for T_{1s}, T_{1n} and perfusion as measured by f/λ.

D. BreastView for display, analysis, interpretation of images.

1. Feature images showing T1n, f/λ image, f/λ error image.
2. Calculation of "suspicion index" and potentially cancerous regions.
3. Pixel cross-registration and comparison between MR image types.

In 1999:

A. Pulse sequences that are compatible with a Signa Horizon LX EchoSpeed CV/I system, running LX 8.2.5 system software:

1. Fast SPGR-based arterial spin tagging sequence
2. Odd-number interleaved EPI sequence
3. Interleaved EPI-based arterial spin tagging sequence

B. Imaging processing software:

1. BreastView (further improvements)
2. DispAlls
3. Bayesian analysis of arterial spin tagged image data

In 2000:

A. EPI-based arterial spin tagging sequence, with MT pulse option, for Signa Horizon LX CV/i system.

In 2001:

There were no new key research accomplishments.

In 2002:

There were no new key research accomplishments.

(7) Reportable Outcomes

In 1998:

A. Arterial spin tagging pulse sequence for Version 5.5 of MRI System

B. New breast imaging protocol for Signa Advantage system

C. BreastView for display, analysis, interpretation of images

D. Buonocore MH, Zhu DL, Pellot-Barakat C., Zulim RA. Non-invasive measurement of breast tissue perfusion using arterial spin tagging. Radiology, November 1997, 205 (P): 162.

E. Buonocore MH, Zhu DC. Odd-number hybrid EPI. Proceeding of the International Society for Magnetic Resonance in Medicine, 6th Annual Meeting and Exhibition, on CD-ROM, p. 1967 (1998).

In 1999:

A. Pulse sequences for 8.2.5 MRI System

1. Arterial spin tagging sequence with Fast SPGR Acquisition
2. Odd-number interleaf EPI

3. Arterial spin tagging sequence with Odd-number interleaf EPI acquisition
4. Arterial Spin Tagging sequence with Even-number hybrid EPI acquisition

B. Breast Imaging Protocols for 8.2.5 MRI System

1. Anatomical, spin tagged, and dynamic contrast enhanced breast imaging protocol

C. SGI Graphics Software for Breast image analysis

1. DispAlls (display program for general MRI images)
2. BreastView (improvements for clinical use)

D. Buonocore MH, Zhu DC. High spatial resolution EPI using an odd number of interleaves. Magnetic Resonance in Medicine 41 (6): 1199-1205 (1999).

E. Buonocore MH, Zhu DC, Zulim RA. Analysis software for breast imaging studies. Proceedings of the International Society for Magnetic Resonance in Medicine, 7th Annual Meeting and Exhibition, 3: 2172 (1999).

In 2000:

A. Buonocore MH, Zhu DC. Magnetic resonance arterial spin tagging for non-invasive pharmacokinetic analysis of breast cancer. Poster Presentation and Abstract. Proceedings of the Era of Hope, Dept. of Defense Breast Cancer Research Program Meeting, June 8-11, 2000, Hilton Atlanta and Towers, Atlanta, GA, Vol. 1, page 177.

B. Buonocore MH, Zhu DC, Zulim RA. Magnetic resonance arterial spin tagging for non-invasive pharmacokinetic analysis of breast cancer. Poster Presentation and Abstract. Proceedings of the UC Davis Cancer Center Symposium, Oct 6-7, 2000. UC Davis Cancer Center, Sacramento, CA.

C. David Zhu. PhD Dissertation. Magnetic resonance pulse sequences and analytical techniques for breast cancer detection and cardiovascular flow. UC Davis, Biomedical Engineering. Dec 1999.

D. David Zhu. PhD in Biomedical Engineering, Dec 1999.

E. David Zhu, PhD. Employment as GE Applications Engineer, beginning Jan 2000.

In 2001:

A. Buonocore MH, Zhu DC. Image-based ghost correction for interleaved EPI. Magnetic Resonance In Medicine 45 (1): 96-108 (2001).

In 2002:

A. Zhu DC, Buonocore MH. Breast Tissue Differentiation Using Arterial Spin Tagging. Submitted to Magnetic Resonance in Medicine, Sept 26, 2002. Reviews returned Nov 14, 2002 (Provisionally accepted, pending review of revisions). (see Appendix).

(8) CONCLUSIONS

We developed the necessary pulse sequences for anatomical and functional imaging of breast tissue, and the necessary software for the analysis, display and interpretation of this data. In 1999, we successfully converted the arterial spin tagging pulse sequences to work on a new research MRI system, and made several enhancements. Understanding of the 8.2.5 pulse sequence language on the new system represented a major advance of the project. In 2000, the technical accomplishments over the past three years were documented in a PhD Dissertation, a CD ROM of research software, and in poster presentations. From Sept. 30, 2000 through Sept. 29, 2002 the project was inactive. We requested and received approval for two no-cost extensions, through Sept 29, 2002, for patient recruitment. From Sept 30, 2001 through Sept 29, 2002 a manuscript covering the key accomplishments was prepared and submitted to Magnetic Resonance in Medicine (MRM). This manuscript was provisionally accepted by MRM on November 14, 2002, pending review of revisions.

The integrated nature of the image display and analysis software allows easy and consistent interpretation of both spatial dependencies as well as temporal dependencies of signal changes indicative of disease. The software has been written to allow analysis to be done by a busy clinician without computer expertise. The in-vitro and in-vivo studies done thus far indicate that first and foremost, arterial spin tagging is a sensitive and reliable method for measuring T_1 and parameters related to tissue perfusion. The fact that arterial spin tagging can be easily added to any standard breast imaging protocol, without requiring special nursing or MR technologist expertise, means that it is especially attractive for routine clinical use. Statistical comparisons of contrast-enhanced images versus arterial spin-tagged images were not conclusive. Further evaluation of arterial spin tagging in the clinical setting is recommended. The Clinical co-investigator and their patient recruitment mechanisms should be established and reliable.

(9) REFERENCES

From 1998:

For a complete listing of references by other authors that are pertinent to the background and significance of the proposal, refer to the 1998 Annual Report.

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Buonocore MH, Zhu DC, Zulim RA. Analysis software for breast imaging studies. Proceedings of the International Society for Magnetic Resonance in Medicine, 7th Annual Meeting and Exhibition, 3: 2172 (1999).

References authored by PI in 2000:

Buonocore MH, Zhu DC. Magnetic resonance arterial spin tagging for non-invasive pharmacokinetic analysis of breast cancer. Proceedings of the Era of Hope, Dept. of Defense Breast Cancer Research Program Meeting, Vol. 1, page 177 (2000).

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(11) LIST OF PERSONNEL RECEIVING PAY

Michael H. Buonocore, MD-PhD

David C. Zhu, PhD

Rebecca C. Zulim, MD

(12) APPENDIX

Year 2002 Appendix material (attached):

Manuscript submitted to Magnetic Resonance in Medicine (MRM) (39 PAGES)

MRM Reviewer's comments regarding Manuscript (5 PAGES)

Letter requesting no-cost extension for Year 2002. (2 PAGES)

Refer to Appendix of 1998 Annual Report for the Following:

The regression method derived in this project resolves a key confound that is present in all arterial spin tagging sequences, that of the mismatch of the slice profiles of the inversion and excitation RF pulses.

Derivation of semi-log linear regression method.

Proof that semi-log linear regression method eliminates slice profile mismatch effects.

Detailed notes written during scanning of phantom, normal subject, and patients.

Refer to Appendix of 1999 Annual Report for the Following:

Documentation regarding approved Budget Changes (pages 24-33).

Documentation regarding change of Co-Investigator to PD Schneider, MD on the Human Subjects Protocol and Consent. Documentation regarding temporary change of patient recruitment to Kaiser Hospital. (pages 33-50).

Copy of publication, Buonocore MH, Zhu DC. High spatial resolution EPI using an odd number of interleaves. Magnetic Resonance in Medicine 41 (6): 1199-1205 (1999). (pages 51-57)

Refer to Appendix of 2000 Annual Report for the Following:

Replications of Posters presented in 2000, 11% of full size) (Pages 15-16)

PhD Dissertation, By D. Zhu (Title, Prefaces, Part I, Appendices A-D,F, G, Pages 17-179).

Refer to Appendix of 2001 Annual Report for the Following:

One-year no-cost extension approval (Administrative Agreement effective Sept 30, 2001 through Sept 29, 2002), including justification of request.

Breast Tissue Differentiation Using Arterial Spin Tagging

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ABSTRACT

An arterial spin tagging pulse sequence has been developed to measure T_1 and relative blood perfusion. This full sequence is composed of a Selective tagging, a Non-selective tagging and a Non-tagging sequence. The perfusion quantification error due to imperfect inversion and acquisition slice profiles has been addressed in the literature. In this work, the error is reduced through the application of optimized SLR RF pulses and a semi-log linear regression data-processing technique. A threshold approach based on the breast tissue T_1 and relative blood perfusion is introduced to show that these two parameters can be applied to breast tissue differentiation and potentially cancer detection.

Key Words

Spin Tagging

Spin Labeling

Blood Flow

Perfusion

Breast

T_1

INTRODUCTION

An arterial spin tagging pulse sequence has been developed to measure T_1 and relative blood perfusion. These two parameters have been used as the primary factors in the technique of breast tissue differentiation proposed in this work. The perfusion quantification error due to imperfect inversion and acquisition slice profiles is reduced through the application of optimized Shinnar Le-Roux (SLR) RF pulses and a semi-log linear regression data-processing technique (1-6).

Malignant tumors induce high-level angiogenesis resulting in the increase of vascularity (7). The rapid growth of malignant tumors suggests high metabolic rates at the tumors, which require an increased supply of nutrients and oxygen as well as the increased effort to remove the waste materials. Therefore, higher blood perfusion and blood volume percentage at malignant tumors are expected (8-10). High water content leads to a long MR spin-lattice relaxation time T_1. Therefore, T_1 and relative blood perfusion can be used as two important factors in determining the breast cancer malignancy. The method of separating normal from abnormal tissue introduced in this work has been based on the expectation that malignant tumors have higher water content than normal tissues and have higher perfusion than both normal tissues and benign lesions.

BACKGROUND

The primary goal of this arterial spin technique is to measure perfusion, which is defined as the milliliters of arterial blood delivered per second per milliliter of tissue (11). Capillaries penetrate each voxel in various directions. Therefore, perfusion represents the combined activity

of the flows of the capillaries and other small vessels within a voxel. The Kety-Schmidt model is used to approximate the activity of the water molecules. In this model, water molecules in blood vessels entering a region of breast tissue mix thoroughly with water molecules outside the vessels before they leave the region (12-14). The Bloch Equation for the water magnetization at a slice of tissue after any RF perturbation has been deduced by Detre et al (15)

$$\frac{dM(t)}{dt} = \frac{M_0 - M(t)}{T_1} + fM_a(t) - fM\frac{M(t)}{\lambda} \qquad [1]$$

where,

$M(t)$ = the longitudinal water magnetization of a voxel of tissue at time t,

M_0 = the value of $M(t)$ under fully relaxed conditions,

T_1 = the spin-lattice relaxation time constant of the tissue,

M_a = the longitudinal water magnetization of arterial blood from outside of the slice measured,

f = perfusion in ml of arterial blood per second per ml of tissue (with dimensions of sec^{-1}),

λ = the ratio of water concentration between breast tissue overall and the arterial blood within it, specifically, (moles of water per ml of tissue)/(moles of water per ml of arterial blood).

The above equation does not include the magnetization transfer terms presented in the later publication by Detre et al (16).

Theory of Pulse Sequence Design

Various spin tagging techniques have been used to estimate perfusion f (or

f/λ)(15-20). The various techniques are all based on three different spin states: equilibrium, saturation and inversion. They can also be categorized as on-slice and off-slice tagging sequences.

The arterial spin tagging method presented in this paper is based on two of these three states: the equilibrium and inversion, which should give the maximum spin signal contrast. On-slice instead of off-slice spin tagging has been chosen so that the measurement is sensitive to the perfusion effect from both sides of the acquisition slice.

Parameters T_1 and f/λ in Eq. [1] are estimated from two spin tagging sequences (the Selective and Non-selective sequences) and the Non-tagging sequence. One slice is investigated at a time. It is referred to as the slice of interest in the following discussion. For the Selective sequence, spins in the slice of interest are inverted first. Then the signal corresponding to the overall spin magnetization from the same slice is acquired at later various times to obtain a good spin recovery curve. Compared to the Selective sequence, the only difference for the Non-selective sequence is that spins are inverted within the entire sensitive volume of the RF transmit coil. For the Non-tagging sequence, there is no spin inversion before acquisition.

During the Selective sequence, since the spins entering the slice of interest are not perturbed, they are in equilibrium. Then,

$$M_a(t) = M_a^0$$

where,

M_a^0 = the value of $M_a(t)$ under the fully relaxed condition.

In the Kety-Schmidt model, the spins in the arterial blood entering the slice are assumed to be able to mix thoroughly with spins in the surrounding breast tissue before leaving the slice (12-14). Thus in equilibrium,

$$f M_a^0 = f \frac{M_0}{\lambda}$$

Eq. [1] then becomes

$$\frac{dM(t)}{dt} = M_0(\frac{1}{T_1} + \frac{f}{\lambda}) - M(t)(\frac{1}{T_1} + \frac{f}{\lambda}) \qquad [2]$$

Eq. [2] has the form of the standard Bloch Equation

$$\frac{dM(t)}{dt} = \frac{M_0 - M(t)}{T_{1s}}$$

with

$$\frac{1}{T_{1s}} = R_{1s} = \frac{1}{T_1} + \frac{f}{\lambda} \qquad [3]$$

where T_{1s} is the apparent spin-lattice relaxation time measured through the Selective sequence. The subscript "s" denotes the T_1 and the R_1 values measured through the Selective sequence.

During the Non-selective sequence, spins are inverted within the entire sensitive volume of the RF coil. The spins inside and outside the slice of interest thus have the same magnetization. Then

$$f M_a(t) = f \frac{M(t)}{\lambda}$$

and Eq. [1] becomes

$$\frac{dM(t)}{dt} = \frac{M_0 - M(t)}{T_1}$$

The T_1 measured in this case is the true T_1 without the influence of blood flow, which is denoted as

$$T_{1n} = T_1 \qquad [4]$$

and

$$R_{1n} = \frac{1}{T_{1n}} \qquad [5]$$

The subscript "n" denotes the T_1 and the R_1 values measured through the Non-selective sequence, distinguishing them from the Selective sequence.

Based on the R_{1s} and R_{1n} values obtained from the two tagging sequences, the relative perfusion

$$\frac{f}{\lambda} = R_{1s} - R_{1n} \qquad [6]$$

The term f/λ is the fraction of water replaced per second in a voxel in the direction perpendicular to the slice. Compared to normal breast tissue and benign lesions, a higher f/λ is expected in malignant tumors.

METHODS

Arterial Spin Tagging Pulse Sequence Implementation

For the arterial spin tagging sequence, an inversion RF pulse is applied first to tag the spins, then data is acquired for the entire image using a fast SPGR (SPoiled Gradient Recalled) symmetric-k space data acquisition scheme (Fig. 1). Data acquisition starts at the k space line closest to $k_y = 0$, and then alternates below and above this k_y line until the lowest and highest k_y lines. This allows the signal of the reconstructed image to have the highest weighting on the data points at the beginning of the acquisition. Thus, the effective time of inversion can have a wide range to map the T_1 recovery curve.

For the Selective sequence, the slice of inverted magnetization is created by applying an SLR inversion pulse in the presence of the slice selection gradient. For the Non-selective sequence, by applying this SLR inversion pulse without an associated slice selection gradient, a non-selective slab containing inverted spins within the entire sensitive volume of the transmit RF coil is created. The data acquisition for the Non-tagging sequence is designed simply by setting the amplitude of the inversion RF pulse and the associated Z gradient pulse to zero, and thus keeping the same timing as the other two sequences.

An optimized RF inversion pulse and an optimized RF acquisition pulse were designed based on the Shinnar Le-Roux (SLR) algorithm (21). The goal is to achieve sharp rectangular slice profiles so that the spins being tagged are basically the spins being measured with the Selective sequence. This inversion pulse is a maximum-phase pulse with 15.6 ms pulse width, 0.95 kHz bandwidth, 1.50% ripple in pass band, 0.40% ripple in stop band and 180^0 flip angle. This acquisition pulse is a spin-echo linear-phase pulse with 6.4 ms pulse width, 1.25 kHz bandwidth, 5% ripple in pass band, 5% ripple in stop band and 10^0 flip angle (Fig. 2). To reduce the impact on the overall scan time, the acquisition pulse cannot be too long and thus its slice profile is less ideal than the inversion pulse. The slice profile issue that can contribute to perfusion quantification error will be addressed in data processing.

In each scanning session, approximately 10 equally spaced coronal slice locations in the breasts are imaged with a total scan time of approximately 25 minutes. Both breasts are scanned simultaneously. At each slice location, 61 images are acquired sequentially with a repetition time of 2.7 sec using the arterial spin tagging sequence (Fig. 3). Twenty-eight images are acquired through the Selective sequence, and then the same number of images through the Non-selective sequence and then five images through the Non-tagging sequence. For either the Selective or

Non-selective sequence, for the total 28 images, seven different choices of inversion time (TI_{br}'s) are used. Four images are acquired at each choice of inversion time.

Half phase field of view data acquisition has been used to achieve the necessary high resolution without any sacrifice of the scan time. The field of view (FOV) in the Y direction is only half of that in the X direction. This takes advantage of the rectangular FOV in bilateral breast imaging.

Numerical Technique for f/λ Estimation

The value of f/λ is the difference between the R_{1s} and R_{1n} values as expressed in Eq. [6]. At each pixel, all dynamic images are used to calculate the R_{1s} or R_{1n} value based on a statistical semi-log linear regression technique. This technique not only provides the necessary statistical information for analysis; it also reduces the perfusion quantification error due to the uncertainty of the effective *TI*'s and the geometric mismatch between the inversion and acquisition slice profiles.

This technique has been developed based on the comparison between the signal from non-inverted spins at the Non-tagging sequence, and the signal from inverted spins at the Selective or Non-selective sequence (Fig. 4). For either tagging sequence, the last three of the four acquired images at each choice of *TI* are nearly at steady state and are extracted for analysis. For the Non-tagging sequence, the last three of the five acquired images are nearly at steady state and their mean is used for analysis. Using the mean of three images instead of a single image helps to improve the signal-to-noise ratio (SNR).

The semi-log linear regression equations, which are derived in the Appendix, are shown below based on two arbitrary data points (the *i*th and *j*th data points) of the T_1 recovery curve:

$$R_{1s} = \frac{1}{T_{1s}} = - \frac{\ln(S_{nt} - S_{sel}(i)) - \ln(S_{nt} - S_{sel}(j))}{TI_{br}(i) - TI_{br}(j)} \quad [7]$$

$$R_{1n} = \frac{1}{T_{1n}} = - \frac{\ln(S_{nt} - S_{non}(i)) - \ln(S_{nt} - S_{non}(j))}{TI_{br}(i) - TI_{br}(j)} \quad [8]$$

where

S_{nt} = the average signal intensity at a pixel from the steady-state images from the Non-tagging sequence,

$TI_{br}(i)$ or $TI_{br}(j)$ = the starting time for image data acquisition after spin inversion at the ith or jth timing condition,

$S_{sel}(i)$ or $S_{sel}(j)$ = the signal intensity at a pixel for a steady-state image at the ith or jth timing condition of the Selective sequence,

$S_{non}(i)$ or $S_{non}(j)$ = the signal intensity at a pixel for a steady-state image at the ith or jth timing condition of the Non-selective sequence.

The TI_{br} defined in the sequence (Fig. 1) is used in the above equation instead of TI (time of inversion) as in Eq. [A8]. During the Selective or Non-selective sequence, signal is acquired along the recovery curve for the multiple phase-encoding steps. Although the first encoding step (at TI_{br}) is the center of k space, the effective TI is shifted from TI_{br}. The amount of shift depends on the T_1 of the pixel and the section of the recovery curve. The subtraction of $TI_{br}(i)$ and $TI_{br}(j)$ eliminates the TI shift contributed by the pixel T_1. Thus, the R_{1s} or R_{1n} calculation error due to the uncertainty of the effective TI's is reduced through the subtraction of $TI_{br}(i)$ and $TI_{br}(j)$.

Eq. [7] also reduces the R_{1s} (or T_{1s}) quantification error due to the geometric mismatch between the inversion and data acquisition slice profiles. The T_{1n} quantification does not have this slice profile mismatch issue because the RF inversion pulse inverts spins within the entire

sensitive volume of the RF transmit coil. For the Selective sequence, the geometric mismatch between the inversion and acquisition slice profiles can lead to signal contamination by signal from non-inverted or partially inverted spins. Assuming the RF inversion pulse is so optimized that the fraction of partially inverted spins can be neglected, the measured signal can be modeled as

$$S_{sel_{meas}} = (1 - err) \cdot S_{sel} + err \cdot S_{nt} \qquad [9]$$

where,

S_{sel} = the signal of a pixel if there is no slice profile mismatch,

$S_{sel_{meas}}$ = the signal of the same pixel measured,

err = the fraction of error due to slice profile mismatch.

The above model approximates the effect of a sharp rectangular inversion slice profile and a less ideal acquisition slice profile that have been designed in this sequence.

Based on the above model, the following is derived in the Appendix (Eq. [A10]):

$$\ln(S_{nt} - S_{sel}(i)) - \ln(S_{nt} - S_{sel}(j)) = \ln(S_{nt} - S_{sel_{meas}}(i)) - \ln(S_{nt} - S_{sel_{meas}}(j))$$

Therefore, either S_{sel} or $S_{sel_{meas}}$ can be used to calculate R_{1s} through Eq. [7]. In other words, by applying the semi-log linear regression method, the problem due to geometric mismatch between the inversion and acquisition slice profiles is eliminated. For simplicity of the notations, the subscript "*meas*" has not been used in Eqs. [7] and [8], but the S_{sel} and S_{non} in these two equations actually represent the signals measured at a pixel.

Methods of Separating Normal from Abnormal Tissue

After the values of T_{1s}, T_{1n} and f/λ at all pixels on each slice are calculated, the corresponding T_1 image, the perfusion image based on f/λ and the error perfusion image based

on the standard deviation of f/λ are constructed. These images are used for the recognition of probable cancer regions through a visualization computer program called BreastView that has been developed on an SGI workstation based on C language, X Window System and Motif 1.2. This problem is implemented with a threshold technique that is discussed following (4,5).

Since a tumor likely grows to several adjacent voxels, these voxels should have similar tissue characteristics. Specifically, they should have high T_1 values that are approximately equal to each other, and high perfusion rates. When a pixel is found to have a high T_1 and a high f/λ, and the standard deviation of the f/λ is low all based on predefined thresholds, this pixel is considered to be a possible cancer pixel. Its surrounding pixels within the same slice and across slices would be checked to see if they have similar characteristics. The level of suspicion, which arbitrarily defined as the chance of being cancerous, for this pixel is calculated based on the percentage of its surrounding pixels (including this central pixel) containing the similar suspicious characteristics. For a typical pixel, there is a total of 27 pixels to check. For a pixel on an edge slice, there is a total of 18 pixels to check. A 5% contribution from the background is always applied. For example, if a suspected cancer pixel has six adjacent pixels with similar characteristics out of the 27 surrounding pixels, its level of suspicion is 30.9%. By applying this method to all pixels in all slices, maps of suspicion are created. If a pixel has a level of suspicion exceeding a cutoff value, such as 20%, this pixel would be labeled as a probable cancer pixel.

Phantom and In-vivo Studies

The capability of the arterial spin tagging sequence to measure T_1 and perfusion has been verified through studies with a flow phantom, normal subjects with normal breasts, and patients with abnormal breast masses. Most of these studies were performed on a Signa Advantage 1.5T GE MR system and the rest were performed on a Signa Horizon LX 1.5T GE MR system (GE

Medical Systems Inc., Milwaukee). A dual phased array breast imaging RF receiving coil (Medical Advance Inc., Milwaukee) was used for the breast studies.

These parameters have been used for all studies: 9.244 ms *TE*, 16.62 ms of time of repetition for the phase encoding steps, ±31.25 kHz receiving bandwidth, 10° flip angle, 3 mm slice thickness, 34 cm × 17 cm field of view (FOV), and 256 × 120 matrix resolution. The time of inversion starts with 615 ms, decrements to 15 ms with a step size of 100 ms.

Perfusion studies using a controllable flow phantom were the first set of verification studies done. A flow phantom was assembled from a kidney dialysis cylinder. This dialysis cylinder is composed of artificial capillaries with membranes that allow the exchange of molecules during dialysis for a kidney patient. Water molecules and small ions such as manganese and chlorine ions that were used in this experiment can move freely through these membranes. It has a length of 25 cm, an internal diameter of about 5 cm, about 1000 capillaries and an approximate λ of 0.15. The fluid used in the phantom was purified drinking water doped with manganese chloride to have a T_1 value of approximately 895 ms, which is within the range of T_1 value of tissue. For the convenience of physical measurement, the perfusion of the flow phantom was only verified in one direction, instead of multiple directions that occur in actual tissue. The flow went through the capillaries from one end of the dialysis cylinder. The flow was fed through long rubber tubes, and was driven by an external electrical mechanical pump outside the magnet room. The flow rate was controlled by adjusting the mechanical pump and was measured using a stop watch and a graduated cylinder.

Eighteen subjects participated in the breast imaging studies. All volunteers signed the consent form of research agreement that had been approved by the Institutional Review Board at the University of California, Davis. At each study, some simple but effective procedures were

used to reduce motion artifacts: (1) the volunteer would be strapped on the scan table in a prone position; (2) the volunteer was instructed not to move and to breathe smoothly during scanning. The arterial spin tagging scan was performed in the coronal view for each study. Besides the arterial spin tagging scan, other examinations using traditional clinical techniques were also done. A T_1-weighted multi-slice spin-echo axial scan was used as a localizer to provide the overview of the whole breasts and neighboring tissues and to help detect the existence of any abnormal mass. A fast spin echo coronal scan with proton density-weighted and T_2-weighted dual echoes was used to provide the traditional clinical breast images. The slice locations of these images were the same as those of the arterial spin tagging sequence. After the imaging study, biopsy was performed on all patients with benign and malignant masses except one benign case.

RESULTS

Phantom Studies

The flow phantom studies showed a clear linear relationship between f/λ measured with the arterial spin tagging technique and the actual flow applied within the range of tissue perfusion (Fig. 5).

Human Subject Studies

Eighteen subjects, including 11 patients, participated in the breast studies. Three patients and two volunteers were eliminated from the analysis because the studies were not done according to protocol, or there was excessive motion during scanning, or the abnormal mass was too close to the chest wall to be measured reliably, or no patient biopsy was performed to confirm the results of the MR study. There were a total of 13 useful cases left for analysis,

including three cases of normal breast, eight cases of benign lesions, and two cases of malignant masses. Three sample case studies (one with normal breasts, one with benign abnormal masses, and one with malignant tumors) are presented first. Then a summary of the studies is followed.

1. Normal

In this study, all images acquired showed well-separated fat and non-fat regions. Regions of interest (ROIs) can be easily isolated for the characteristic comparison between fat and non-fat tissues of the breast. The ROIs with the size of 35 mm^2 have been identified from all 10 slices acquired from the arterial spin tagging sequence. The f/λ and T_{1n} distribution for this study is summarized in Table 1. Voxels containing non-fat tissue in general have higher T_{1n} and f/λ values than voxels containing fatty tissue.

2. Benign Abnormal Mass

A rod-shape abnormal mass was seen in a breast of a healthy volunteer. Based on 10 years of monitoring, this mass had been diagnosed to be benign before the perfusion study was performed. ROIs with the size of 35 mm^2 have been isolated from the edge and the center of the abnormal mass as well as non-fat area outside the abnormal mass for the tissue MR characteristic comparison. The f/λ and T_{1n} distribution for these different tissues is summarized in Table 2. For this case study, the lesion center in general has higher perfusion rate (f/λ) than the lesion edge and the non-fat regions.

3. Malignant Tumor

In this study, three slice locations centering around the abnormal mass were studied. The probable cancer regions were identified based on the image processing and visualization techniques discussed earlier and were labeled by color mapping and overlay onto the clinical images (Fig. 6). These regions were close to the abnormal mass that could be palpated, and its

malignancy was later confirmed by needle biopsy. ROIs with the size of 35 mm^2 have been isolated at the tumor, non-fat regions outside the tumor as well as fat tissue for tissue MR characteristic comparison. Fig. 7 shows the f/λ and T_{1n} distribution for these different areas, and can be summarized in Table 3. As shown in Fig. 7, fat can be separated out easily based on T_{1n} value alone because it has T_{1n}'s much lower than those of the other two groups of tissue. The f/λ for fat have a wide range, and thus f/λ does not provide any value for fat tissue recognition. Since tumor tissue is non-fat tissue and should have T_{1n} value at the range of healthy non-fat tissue, the overlap between fat and tumor is minimal. However, to separate tumor tissue from non-fat tissue, both the T_{1n} and f/λ values should be used. For example, as shown in Table 3 and Fig. 7, both the T_{1n} and f/λ values at tumor tissue are relatively higher than those at non-fat tissue, but with some overlap.

4. Human Subject Study Summary

For all human subject studies, the probable cancer pixels were identified based on the following criteria:

T_{1n}: > 0.5 sec

f/λ: > 0.1 sec^{-1}

STD of f/λ: < 0.1 sec^{-1}

Suspicion level threshold: > 20%.

The above T_{1n} threshold was chosen based on the comparison of T_{1n} distribution between fat and non-fat tissue of the normal cases. The above f/λ and STD of f/λ thresholds were chosen based on the f/λ distribution of the malignant cases. The suspicion level threshold was chosen based on the comparison between malignant and benign cases. These thresholds have been based on observation instead of vigorous statistical analysis, which needs more case studies.

The results of 13 studies are summary shown in Table 4. Based on this table, the number of true positive (TP) is 2; the number of false negative (FN) is 0; the number of false positive (FP) is 3 and the number of true negative (TN) is 8. Therefore, the true-positive fraction or sensitivity is 100%. The false-positive fraction is 27.3%. The specificity is 72.7%.

DISCUSSION

The flow phantom studies show that the arterial spin tagging sequence can be applied to measure the perfusion activity accurately. The human subject studies shows that the arterial spin tagging sequence and the analytical technique can be applied to tissue classification and tumor identification. The results from the human subject studies confirm the expectation that malignant tumors have higher water content than normal tissues and have higher perfusion than both normal tissues and benign lesions.

The probable cancer pixel identification based on the thresholds of T_{1n}, f/λ, STD of f/λ and the suspicion level provides an approach for cancer recognition in this work. This technique is most useful if the number of cases studied is limited. However, if a large pool of case studies is available, statistically techniques, such as a Bayesian decision technique, can be applied to cancer identification (5,22). The Bayesian technique can be extended to the ROC (receiver operating characteristic) curve that is commonly used for the evaluation of a diagnostic algorithm in radiology.

For the Selective sequence, a same slice thickness is applied for both inversion and acquisition to increase the sensitivity to perfusion. This avoids the transit delay that occurs between the tagging and acquisition regions if the inversion slice is thicker than the acquisition slice (23). However, applying the same slice thickness leads to the issue of slice-profile

mismatch. This issue has been addressed by Frank et al (24) and recently Schepers et al (25) with an emphasis on RF pulse design, and by Sidaros et al (26) with an emphasis on post processing. In this work, both approaches have been applied through the use of optimized RF pulses and a statistical semi-log linear regression post-processing technique. Schepers et al showed that adiabatic pulses could produce better slice profiles than sinc and SLR pulses. But they also pointed out that adiabatic pulses needed to have long pulse widths to produce good slice profiles. Long pulse widths can lead to more magnetization transfer effect (24), which has been assumed to be relatively small in this paper. Long RF pulses are not practical either to be used as the acquisition pulse in 2D Fast SPGR due to the long total image acquisition. SLR pulses can provide sharp slice profiles with relatively shorter pulse widths and thus have been used in this work. The perfusion quantification error due to slice profile imperfection is reduced through the semi-log linear regression data processing. This technique is different from the technique presented by Sidaros et al, which requires the precise knowledge of the inversion pulses for the offset estimation. The regression technique presented in this paper does not require the prior knowledge of the RF pulse profiles. It only assumes that the signal contamination at the Selective sequence is caused by signal from non-inverted spins. The regression is straightforward and provides the statistical information to justify the confidence level of the f/λ estimation for each pixel.

The fast SPGR based spin tagging sequence as well as the new data analysis technique has some limitation on accurate T_1 and f/λ estimation. The data acquisition has been assumed that it would not disturb the recovery curves of the inverted spins or the equilibrium states of the non-inverted spins. To make this assumption more realistic, it is worthwhile to investigate the approaches of replacing the 2D fast SPGR data acquisition scheme with an echo planar or spiral

data acquisition scheme. In echo planar imaging (EPI) or Spiral imaging, only one acquisition RF pulse is used for the complete data acquisition of a whole image. The disturbance due to the acquisition RF pulses to the recovery curves of the inverted spins or the equilibrium of the non-inverted spins would be smaller. Since EPI or spiral imaging is faster than 2D fast SPGR, the total scan time would be shorter also. However, both EPI and Spiral are sensitive to system imperfection such as eddy currents. The fast SPGR is less sensitive to system imperfection and thus was chosen as the data acquisition scheme in this work.

In MRI, the technique that is widely used for breast cancer detection is MR dynamic first-pass contrast enhancement (commonly named Magnetic Resonance Mammography). This technique has shown its capability in distinguishing between malignant and benign breast lesions (27). However, it cannot be used in screening, even within defined high-risk sub-populations (e.g. patients with dense breasts), due to the high cost of contrast material and its administration. It also has to finish the scan within a limited time to avoid the washout of contrast material, and thus the resolution and SNR are limited. The arterial spin tagging technique presented does not need contrast materials and potentially can be used as a screening tool. It may provide more sensitive and specific assessment of tissue parameters, at higher spatial resolutions, by its ability to improve signal to noise ratio (SNR) over a reasonable scan time. The arterial spin tagging pulse sequence and analytical techniques presented may be suitable for all specific clinical indications that have been reported for first-pass contrast enhanced imaging. They may in fact be more convenient and equally reliable for identifying the regions of tissue changes that give rise to contrast enhancement. However, contrast enhancement is regarded as essential in MRI breast evaluation, and is unlikely to be supplanted. The recommendation is to perform the first-pass

contrast enhancement comparison study along with all the arterial spin tagging studies. This would allow the direct comparison in accuracy, precision as well as the ease of application.

APPENDIX

Derivation of the Semi-log Linear Regression Equations

In the derivation of the linear equations (Eqs. [7] and [8]), the following ideal situation is assumed: The acquisition RF pulse causes such a small flip angle that its continuous application for all the phase-encoding steps does not disturb the natural recovery of the inverted spins of a tagging sequence and the equilibrium of the spins at the Non-tagging sequence.

Given this assumption, for a spin tagging sequence, the steady-state longitudinal magnetization at the end of each TR period just before the next inversion pulse can be stated as:

$$M_{t0ss} = M_0 \frac{1-e^{-R_1 TR}}{1+e^{-R_1 TR}} \qquad [A1]$$

where,

M_{t0ss} = the steady-state longitudinal magnetization at the end of each TR period,

M_0 = the longitudinal magnetization under fully relaxed conditions,

$$R_1 = \begin{cases} \frac{1}{T_{1s}} & \text{for the Selective condition} \\ \frac{1}{T_{1n}} & \text{for the Non-selective condition} \end{cases},$$

TR = the repetition time.

The longitudinal magnetization at time t after the spin inversion at steady-state is

$$\begin{aligned} M_t(t) &= M_0(1-e^{-R_1 t}) - M_{t0ss}e^{-R_1 t} \\ &= M_0(1-\frac{2e^{-R_1 t}}{1+e^{-R_1 TR}}) \end{aligned}$$

or

$$M_t(t) = M_0(1-\frac{2e^{-R_1 t}}{1+e^{-R_1 TR}}) \qquad [A2]$$

As a result, the signal measured at echo time *TE* is

$$S_t = M_0(1-\frac{2e^{-R_1 TI}}{1+e^{-R_1 TR}})\sin(\theta)e^{-\frac{TE}{T2}} \qquad [A3]$$

where,

TI = the time of inversion,

TE = the time of echo at each acquisition period,

θ = the acquisition RF flip angle.

For the spin Non-tagging sequence, based on the given assumption, the longitudinal magnetization $M_{nt}(t)$ at any time *t* stays at equilibrium. Specifically,

$$M_{nt}(t) = M_0 \qquad [A4]$$

The signal measured at echo time *TE* becomes

$$S_{nt} = M_0 \sin(\theta)e^{-\frac{TE}{T2}} \qquad [A5]$$

Thus,

$$\frac{S_t}{S_{nt}} = 1-\frac{2e^{-R_1 TI}}{1+e^{-R_1 TR}} \qquad [A6]$$

Then,

$$\frac{S_{nt}-S_t}{S_{nt}} = \frac{2e^{-R_1 TI}}{1+e^{-R_1 TR}}$$

Thus,

$$\frac{S_{nt} - S_t(i)}{S_{nt} - S_t(j)} = \frac{e^{-R_1 TI(i)}}{e^{-R_1 TI(j)}} = e^{-R_1(TI(i)-TI(j))} \qquad [A7]$$

where,

$TI(i)$ = the time of inversion at the ith TI cycle,

$S_t(i)$ = the signal at a pixel when $TI(i)$ is used,

$TI(j)$ = the time of inversion at the jth TI cycle,

$S_t(j)$ = the signal at a pixel when $TI(j)$ is used.

Then,

$$\ln(S_{nt} - S_t(i)) - \ln(S_{nt} - S_t(j)) = -R_1(TI(i) - TI(j))$$

Thus,

$$R_1 = -\frac{\ln(S_{nt} - S_t(i)) - \ln(S_{nt} - S_t(j))}{TI(i) - TI(j)} \qquad [A8]$$

The above equation shows the semi-log linear regression relationship between (S_{nt} - S_t) and TI. It can be applied to both Selective and Non-selective tagging sequences.

RF Slice Profile Mis-match Analysis

From Eq. [9],

$$\frac{S_{sel_{meas}}}{S_{nt}} = (1 - err)\frac{S_{sel}}{S_{nt}} + err$$

And

$$\frac{S_{sel}}{S_{nt}} = \frac{\frac{S_{sel_{meas}}}{S_{nt}} - err}{1 - err}$$

$$1-\frac{S_{sel}}{S_{nt}}=1-\frac{\frac{S_{sel_{meas}}}{S_{nt}}-err}{1-err}$$

$$\frac{S_{nt}-S_{sel}}{S_{nt}}=\frac{1-err-\frac{S_{sel_{meas}}}{S_{nt}}+err}{1-err}$$

$$=\frac{1-\frac{S_{sel_{meas}}}{S_{nt}}}{1-err}$$

Thus,

$$\frac{S_{nt}-S_{sel}(i)}{S_{nt}-S_{sel}(j)}=\frac{1-\frac{S_{sel_{meas}}(i)}{S_{nt}}}{1-\frac{S_{sel_{meas}}(j)}{S_{nt}}}=\frac{S_{nt}-S_{sel_{meas}}(i)}{S_{nt}-S_{sel_{meas}}(j)} \quad [A9]$$

Therefore,

$$\ln(S_{nt}-S_{sel}(i))-\ln(S_{nt}-S_{sel}(j))=\ln(S_{nt}-S_{sel_{meas}}(i))-\ln(S_{nt}-S_{sel_{meas}}(j)) \quad [A10]$$

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FIGURE CAPTIONS

Figure 1. The fast SPGR based arterial spin tagging sequence. The parameter *TR* is fixed at 2.7 sec by default. An inversion tagging RF pulse is applied first, followed by phase encoding steps starting around zero *k* space. The time TI_{br} is changed by changing *t_befiv*. To show the details, the RF acquisition pulses are magnified, and *t_befiv* and TI_{br} are longer than they appear. N_{max} is the total number of k_y lines.

Figure 2. SLR 180^0 inversion and 10^0 data acquisition RF pulses frequency response based on simulation: (a) The near rectangular frequency response based on the longitudinal magnetization for the inversion pulse, and (b) the magnitude of the frequency response based on the longitudinal magnetization and the associated phase for the data acquisition RF pulse.

Figure 3. Image series plot using the fast SPGR based arterial spin tagging sequence. This plot shows the signal at the same pixel across the 61 images acquired using this full sequence. This full sequence is composed of the Selective, Non-selective and Non-tagging sequences. For either the Selective or Non-selective sequence, seven *TI* timing conditions are used. Four repeated images are acquired at each *TI* timing condition. Images are acquired in a continuous manner with a repetition time of 2.7 seconds.

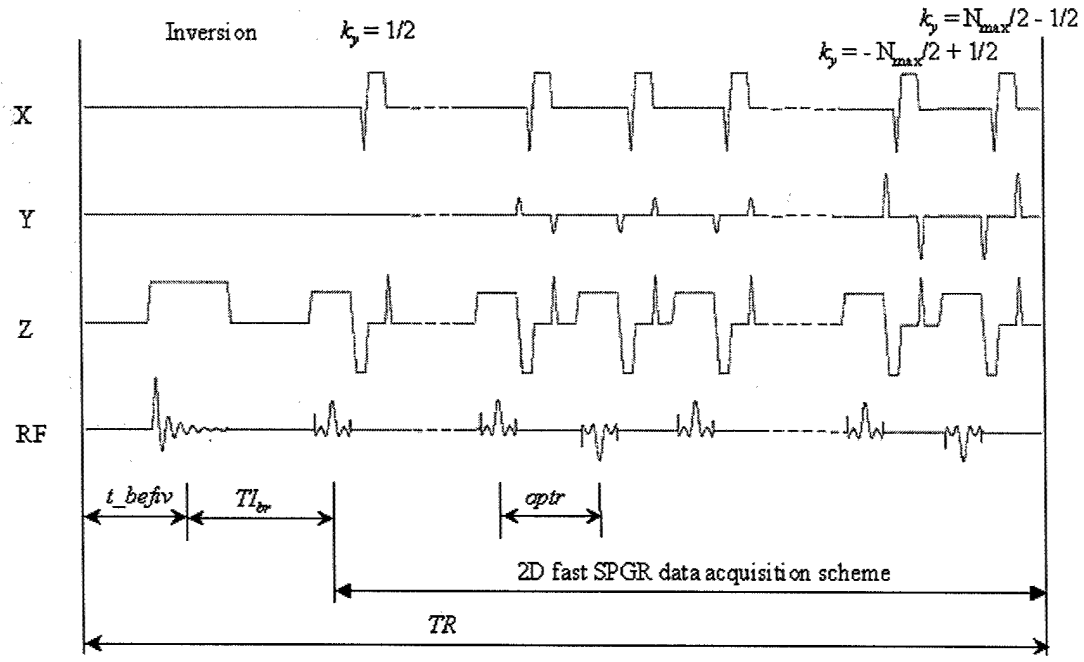
Figure 4. An example of semi-log linear regression for T_1 calculation. This figure shows an example of the application of the semi-log linear regression method in calculating T_1 values (T_{1s} through the Selective sequence and T_{1n} through the Non-selective sequence) and the relative perfusion rate f/λ. TI_{br} is the starting time of image acquisition after the spins are inverted. S_{nt} is

the average signal intensity at one pixel from the last three images at the Non-tagging sequence. S_{sel} is the signal intensity at the same pixel from one of the steady-state images at the Selective sequence. S_{non} is the signal intensity at the same pixel from one of the steady-state images at the Non-selective sequence.

Figure 5. Results from the kidney dialysis phantom perfusion study. The arterial spin tagging sequence was applied at four different low flow rates with 0, 0.0222, 0.0640 and 0.0787 ml/sec/cm^2. The corresponding f/λ values calculated were 0.0251, 0.138, 0.331 and 0.409 sec^{-1}.

Figure 6. Probable cancer region color mapping. The identified suspected cancer pixels are mapped onto the high-resolution traditional clinical MR images according to their corresponding slice locations. These images are from three consecutive 3mm slices with inter-slice distance of 10 mm.

Figure 7. The f/λ and T_{1n} distribution for breast tissue with a malignant tumor.



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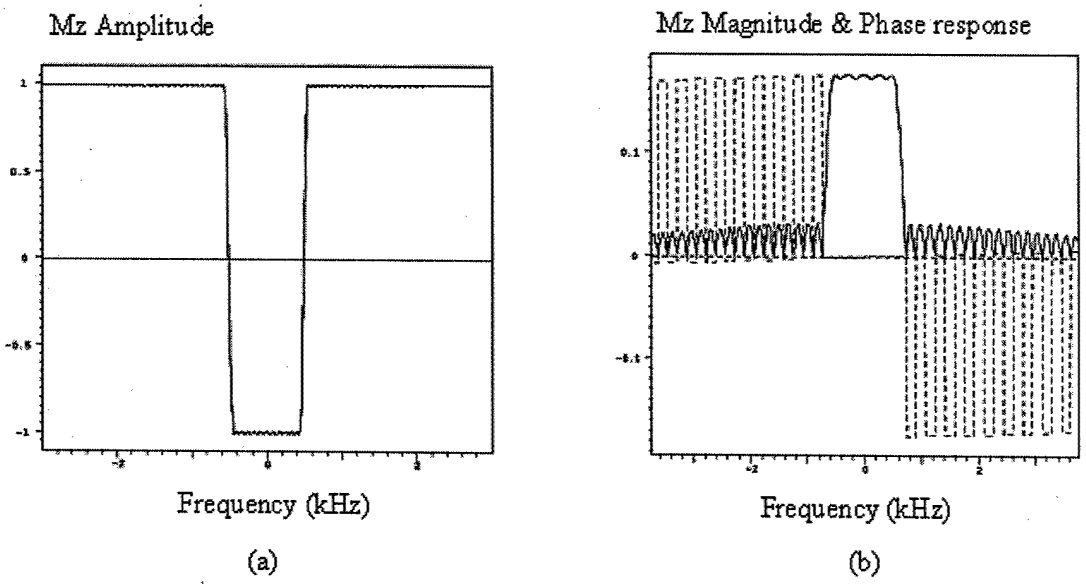

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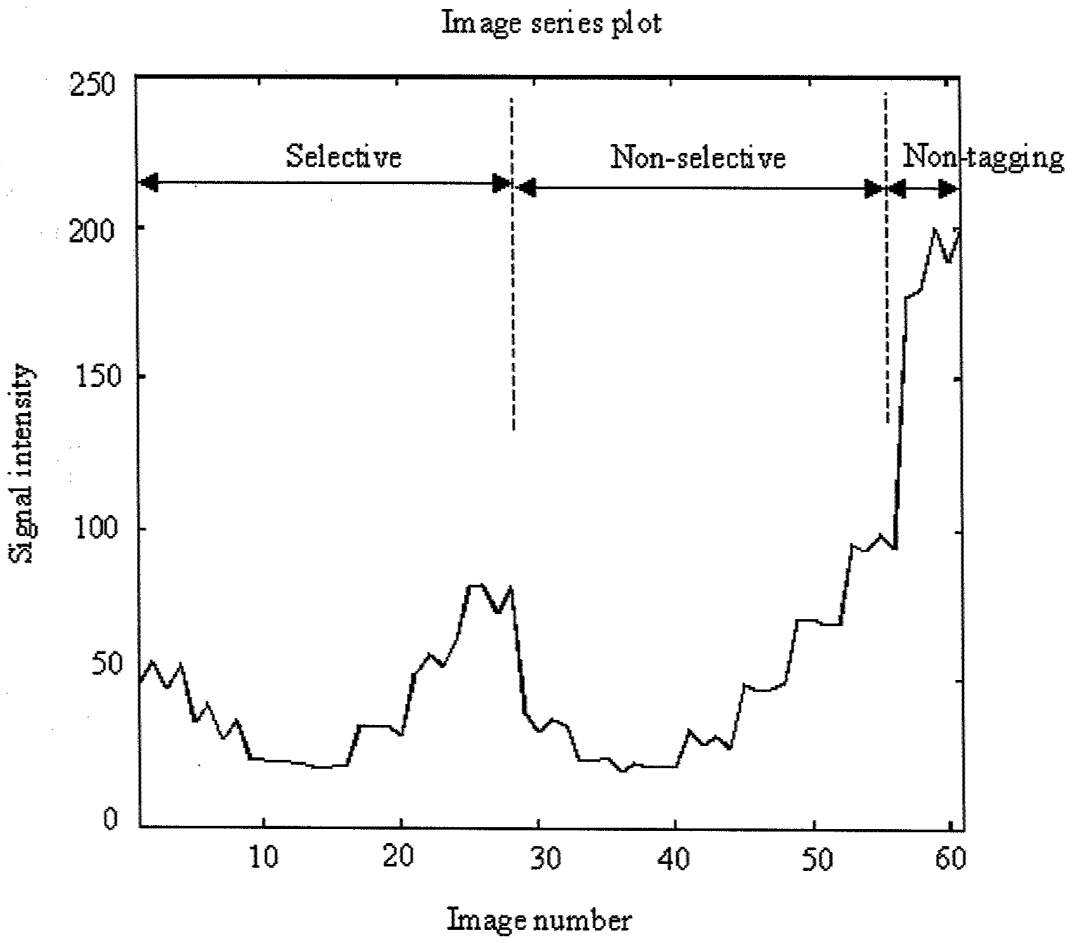

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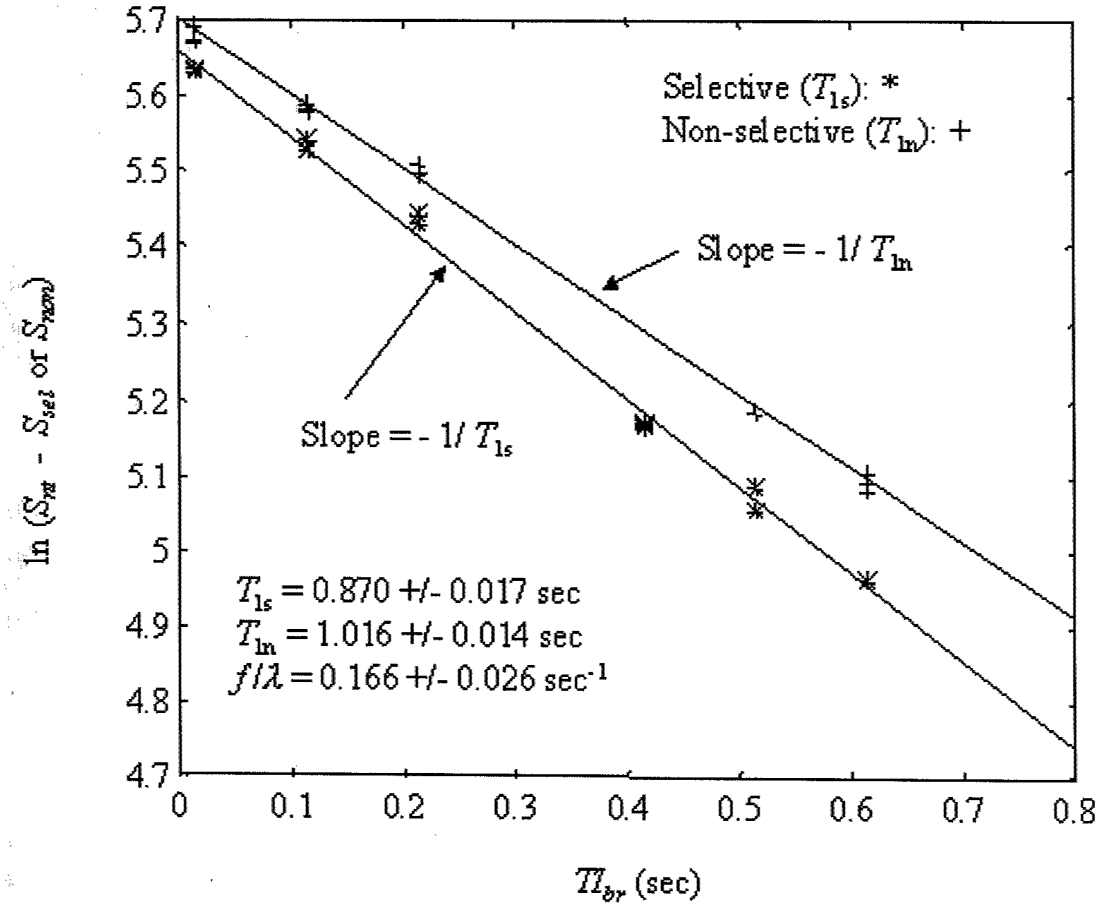

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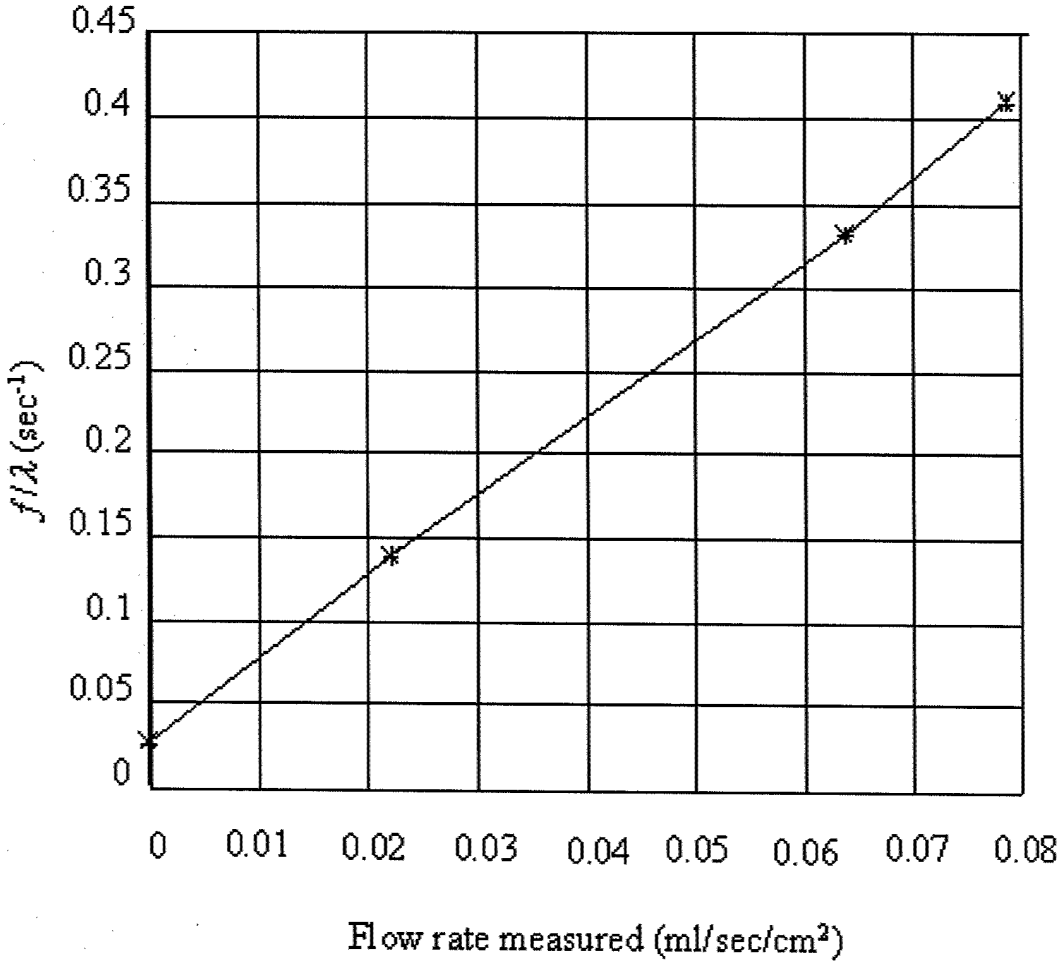

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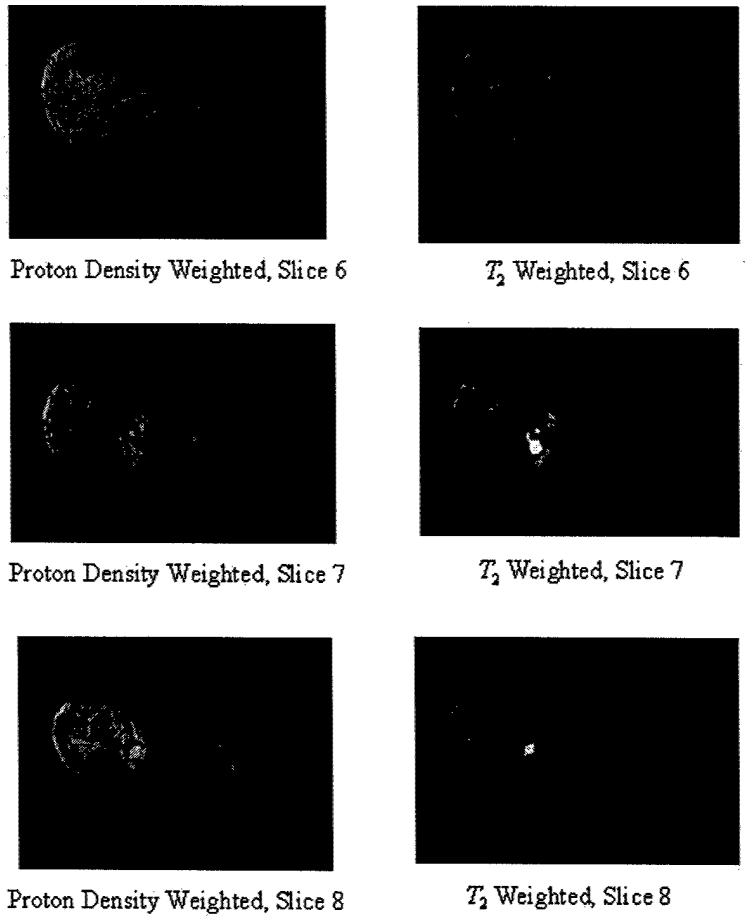

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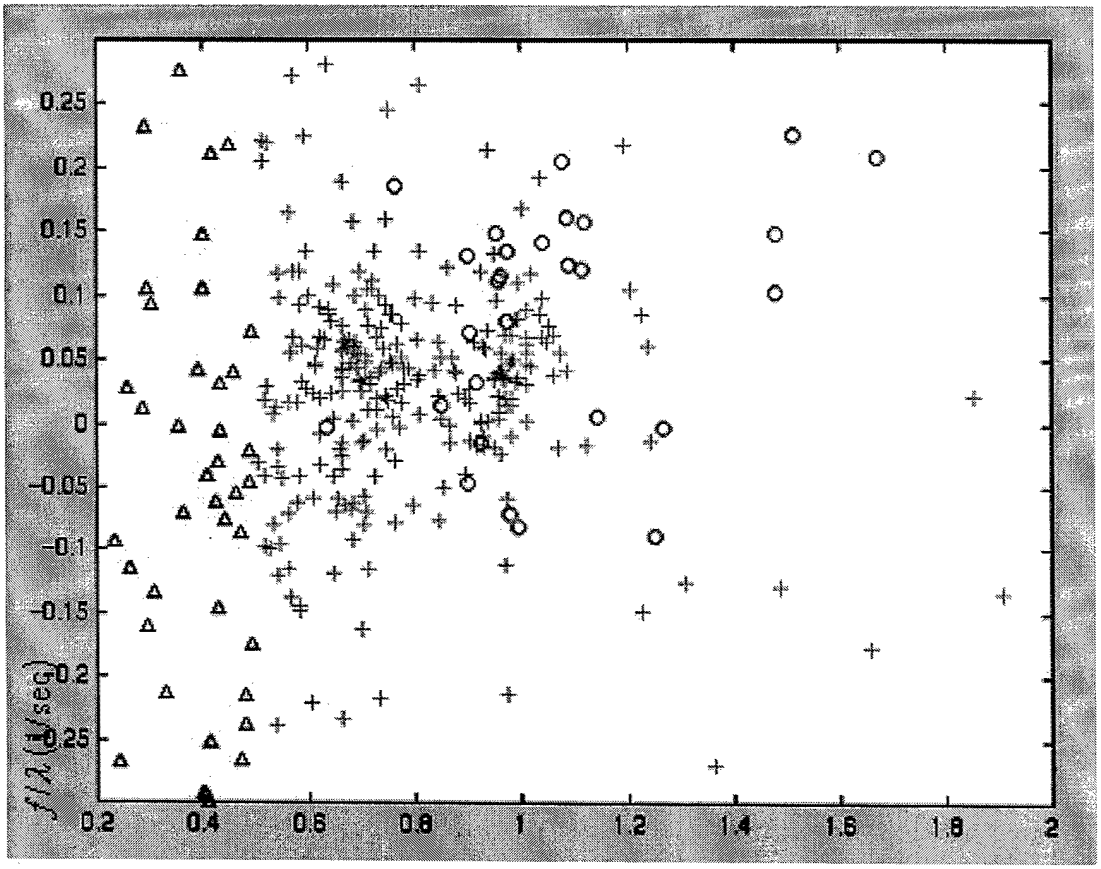

Figure 7. The f/λ and T_{ln} distribution for breast tissue with a malignant tumor.

Table 1. The f/λ and T_{1n} Summary for a Study of Normal Breasts

	Mean of T_{1n} (sec)	STD of T_{1n} (sec)	Mean of f/λ (sec^{-1})	STD of f/λ (sec^{-1})
Fat	0.435	0.207	- 0.005	0.135
Non-fat	1.446	0.403	0.033	0.044

Table 2. The f/λ and T_{1n} Summary for a Study of a Benign Abnormal Breast Mass

	Mean of T_{1n} (sec)	STD of T_{1n} (sec)	Mean of $f/\lambda\ell$ sec^{-1})	STD of $f/\lambda\ell$ sec^{-1})
Lesion Center	0.813	0.053	0.057	0.018
Lesion Edge	0.615	0.140	0.034	0.018
Non-fat Tissue	1.142	0.487	0.013	0.025

Table 3. The f/λ and T_{1n} Summary of a Malignant Breast Tumor Study

	Mean of T_{1n} (sec)	STD of T_{1n} (sec)	Mean of f/λ (sec^{-1})	STD of f/λ (sec^{-1})
Fat	0.385	0.085	-0.177	0.592
Non-fat	0.842	0.392	0.035	0.266
Tumor	1.145	0.372	0.111	0.142

Table 4. Summary of Breast Case Studies

Date of Study	Subject Referred by	Palpable (Yes or No) ?	Seen on Clinical MRI ?	Level of Suspicion Based on T_{1n} and f/λ	Assessment Based on Suspicion Level	Abnormal Mass Type
05/03/97	Physician	No	Yes	Low	Negative	Benign (Fibroadenoma)
05/23/97	Physician	Yes	Indeter-minable	Moderate High	Positive	Malignant (Ductal Carcinoma)
08/01/97	Physician	Yes	No	High	Positive	Malignant (Ductal Carcinoma)
11/15/97	Physician	Yes	No	Low	Negative	Benign
12/10/97	Physician	Yes	No	High	Positive	Benign
04/13/98	Physician	Yes	Indeter-minable	Moderate High	Positive	Benign
07/27/98	Physician	Yes	No	Low	Negative	Benign
08/07/98	Physician	Yes	No	High	Positive	Benign
02/07/97	Herself	No	No	Low	Negative	Normal
03/05/97	Herself	Yes	Yes	Low	Negative	Benign (Fibroadenoma)
07/26/97	Herself	No	No	Low	Negative	Normal
11/16/97	Herself	Yes	Yes	Low	Negative	Benign (Fibroadenoma)
12/14/97	Herself	No	No	Low	Negative	Normal

Normal = normal subject who does not have any tumor based on reliable health history.
Abnormal Mass Type = determined based on biopsy or reliable health history.

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BREAST TISSUE DIFFERENTIATION USING ARTERIAL SPIN TAGGING

David C. Zhu and Michael H. Buonocore

This paper presents the results of using an arterial spin tagging pulse sequence to measure T1 and relative blood perfusion in breast lesions. The sequence consists of a selective tagging, a non-selective tagging, and non-tagging sequence. A Shinnar Le-Roux RF pulse is used to improve the inversion pulse and slice-selection profiles. It is shown that breast tissue T1 and relative blood perfusion can potentially be used to better differentiate between benign and cancerous breast tissue. For benign abnormal mass the lesion center in general has higher perfusion rate than the lesion edge and the non-fat regions in the breast. For a malignant tumor both the T1 and perfusion rate are relatively higher than those in non-fat tissue in the breast. The authors conclude that both T1 and perfusion rate should be used to differentiate malignant from benign breast tissue. In a human study, a probable cancer pixel was based on T1 > 0.5 sec, f/l > 0.1 sec^{-1}, STD of f/l < 0.1 sec^{-1}, suspicion level threshold > 20%. Based on 13 studies this gave a sensitivity of 100%, a false-positive fraction of 27.3%, and a specificity of 72.7%.

This is a well-written paper. I went through most of the mathematical derivations. A good part of the mathematics is from the work of Detre *et al.* I may have missed it but I would have like the authors to highlight the differences in their mathematical development from that of previous work. The authors should consider the following

1. Abstract: Replace SLR with Shinnar Le-Roux (SLR).
2. Page 3: " The primary goal of this arterial spin technique is....." Change to "The primary goal of this arterial spin tagging technique is ....."
3. Eq. [1]: What is fM after the minus sign in this equation?
4. Page 5: "Then the signal corresponding to the overall spin magnetization from the same slice is acquired at later various times to obtain a good spin recovery curve." Rewrite this sentence.
5. Page 8: "The goal is to achieve sharp rectangular slice profiles so that the spins being tagged are basically the spins being measured with the Selective sequence." What happens to spin flowing during the application of the pulse?
6. Page 13: "For the convenience of physical measurement,..." Change to "For the convenience of the physical measurement,...."
7. Page 20: "R1= " A very strange symbol appears after the equal sign.
8. There are errors in the printout of the tables and figures. It may be because I printed the manuscript from a Mac. This may be related to my comment 8.

MAGNETIC RESONANCE IN MEDICINE

Corresp. Author: **Buonocore**

Title: **Breast Tissue Differentiation Using Arterial Spin Tagging**

MS# **MRM-102-6023** Manuscript Category: **full paper**

Referee **2** (for Author Correspondence)

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- ☐ **4 Very good**
- x **3.5**
- ☐ **3 Good**
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Review of manuscript - MRM-102-6023- „Breast tissue differentiation.... " by Buonocore et al.

This is an interesting paper dealing with an important issue of tumor imaging. I think the paper may be accepted after some revisions.

I would like to discuss the following points:

1. Eq. 1 the last term.....- f M M(t)/lambda : I think there is one M too much (most probably a typo).

2. One prerequisite of perfusion measurement by slice selective preparation is that the mean transit time "tau " of spins in the arterial system in the preparation slice is negligible compared to the effect of perfusion on 1/T1, i.e. " f/lambda tau 1 ". Otherwise your Eq. 3 is not valid. In tissues like myocardium the directed blood flow from base to apex and parallel distribution of blood from arteries to capillaries allows perfusion measurement when the slice is perpendicular to the long heart axis. What is the situation in tumors? Can you estimate "tau"? Do you have histological and functional data as relative arterial blood volume and perfusion which give tau as "tau=rel. art. blood volume/Perfusion"? How do your data change when the direction of the slice is changed?

3. A lot of space is used to describe the effect of perfusion on T1 when selective sequences are applied. However this has been done previously in detail (Bauer et al., MRM 38: 917 (1997)) even for the situation of "non thoroughly" mixing of spins, i.e. for arbitrary intra-extracapillary exchange rates. Perhaps this may help to shorten a bit the description.

4. Your derivation of magnetization decay after non-selective sequences (pages 6,7) is not quite correct. The equation "f Ma(t)=f M(t)/lambda" and the further derivation till Eq. 6 are only valid when the relaxation time of blood and the instrinsic relaxation time of tissue are identical. In most cases T1 of blood is longer that the instrinsic T1 of the tissue, hence, for non sel. sequences perfusion leads to a prolongation of the apparent T1. This is derived in - Bauer et al. MRM 35: 43 (1996)- . Based on this paper the general relation between perfusion, sel. and non-sel. T1 of tissue and T1 of blood was obtained by Belle et al. (Eq. 6 in JMRI 8:

1240 (1998)) . This Equation turns into your Eq. 6 for T1arterial=T1n. Perhaps you can show that this is almost the case in your setup.

5. I have problems with the phantom studies (page 13) . You used a dialysis cylinder and you state that water molecules can move freely through the membranes. This suggests that this model is in accordance with the situation in tissue, where you assume a fast mixing of intracapillary and extravascular spins (fast exchange assumption). However, to my knowledge, this is not fulfilled in dialysis cylinders, where the dimensions of the "capillaries" and the intercapillary distance imply that intra-extracapillary mixing is negligible on a time-scale of T1. Didn't you just measure the inflow in the intracapillary compartment? If not, this should become evident in Figure 5 by comparing f/lambda vs. " flow rate (*as you defined it in the Figure 5*) x cross section of all capillaries / cross section of the cylinder". When intra-extracapillary mixing is of relevance the regression line should have a slope of 1. Please analyze the data of Figure 5 according to this suggestion and also provide the cross section of a single capillary.

6. I consider this study as a pilot study with very few patients. Therefore all statements concerning sensitivity and specificity should be drawn very cautiously. You just had 2 cases (page 15) with malignant masses. Therefore I think that the whole statistical discussion (page 17) and comparison with clinical studies (Table 4, by the way: where are these studies taken from?Ref. [27]?) are a bit exaggerated. Instead it would be more useful to compare your perfusion, T1n data in malignant and normal tissue with that of others. Perhaps you can present a table giving these information.

7. Please explain: why is the standard deviation of f/lambda so high when compared to non-fat or tumor tissue. Please provide an error analysis. I think a table like Table 3 is not sufficient. Please provide a scatter diagram/distribution of f/lambda, T1n and STD f/lambda for fat, non fat, benign lesions and malignant masses. Your thresholds (page 16) (which you may insert) should become evident from these figures.

Michael H. Buonocore

From: Fay Yee [FFYee@Research.ucdavis.edu]
Sent: Tuesday, October 16, 2001 8:36 AM
To: Buonocore, Michael
Cc: Jennifer O'Rell
Subject: FW: No-cost extension on DAMD-17-97-1-7030

FYI...the extension will be processed when it is received. Take care... -Fay.

-----Original Message-----
From: Johnson, Marquerita E Ms USAMRAA [mailto:Marquerita.Johnson@DET.AMEDD.ARMY.MIL]
Sent: Tuesday, October 16, 2001 5:04 AM
To: 'Fay Yee'
Subject: RE: No-cost extension on DAMD-17-97-1-7030

The extension has been approved. A modification to that effect will be forthcoming.

Thank you,
Rita Johnson

-----Original Message-----
From: Fay Yee [mailto:FFYee@Research.UCDavis.Edu]
Sent: Monday, October 15, 2001 5:23 PM
To: 'Marquerita.Johnson@DET.AMEDD.ARMY.MIL'
Cc: Buonocore, Michael; Jennifer O'Rell
Subject: FW: No-cost extension on DAMD-17-97-1-7030
Importance: High

Dear Ms. Johnson,

Please consider this email as institutional concurrence of Dr. Buonocore's request below. Please feel free to contact me with any additional concerns.

-Fay Yee
Contracts and Grants Analyst
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-----Original Message-----
From: Michael H. Buonocore [mailto:mhbuonocore@ucdavis.edu]
Sent: Monday, October 15, 2001 10:46 AM
To: Rita Johnson
Subject: No-cost extension on DAMD-17-97-1-7030

Dear Ms. Johnson,

I am writing to request a one year no-cost extension of grant DAMD-17-97-1-7030. During the past year, the project has been inactive, and no funds have been expended. In the paragraphs below I explain the history of project progress, and provide reasons why I believe that the project objectives can be completed over the next year.

Last year at this time (Sept 29, 2000) I received a one year no-cost extension of the grant. At that time, the grant objectives had not been completed because my co-Investigator, Rebecca Zulim, MD (oncology surgeon) who was responsible for recruitment and evaluation of the patients, left the Medical Center. At that time (one year ago), I anticipated that the studies could be completed with the help of a new faculty member in Radiology, Dr. Edward Lee. Dr. Lee and I developed a plan for recruitment that remains a valid approach today.

The project has remained inactive over the past year, due to other difficulties. In late 2000, I anticipated finding another graduate student to continue the efforts of David Zhu, whose PhD dissertation on arterial spin tagging was submitted in last year's annual report. I was hopeful that Gina Belleau, a master's student who had worked with me on imaging of breast viscoelasticity, would accept this work. However, Gina chose to work on another project with me. She is currently employed as a technical writer for two MRI books.

I quickly found that the time that would be required to analyze the breast arterial spin tagging data was much more than I could afford to give. The work of acquiring and analyzing the data required a full time graduate student. My lack of time for analyzing the data was further reduced by my acceptance in July 2000 of the Technical Directorship of MRI for the Radiology Department. Furthermore, in April 2001, I accepted the Technical Directorship of the new Imaging Research Center of the UC Davis Health System. These responsibilities have taken away from time I might have spent on the data analysis.

The Imaging Research Center, a new facility established in July 2001, provides an ideal setting for the breast imaging study. It currently houses a GE 1.5T CV/I system. Trained technical staff and credentialed MRI operators provide all the services needed to carry out the scanning sessions. Prior to July 2001, this system was managed by the Radiology Dept, and was the system on which the breast imaging studies were to be performed. Technical staff and credentialed MRI operators for support of research were not provided under Radiology management, making projects difficult to orchestrate. Therefore, the environment for performing the breast imaging study has greatly improved.

An outstanding biomedical engineering graduate student, Mahmoud Abdulhusain, has this summer begun his PhD dissertation work on arterial spin tagging under my supervision. Mahmoud has taken all four of my graduate MRI courses and is well prepared for research. He will devote the first year of his dissertation work to this arterial spin tagging project.

If you have further questions or need more documentation, please do not hesitate to write or call. Thank you for your consideration. I look forward to hearing from you.

Sincerely,

Mike Buonocore

Cc: Fay Yee, UC Davis Contracts and Grants Office

Michael H. Buonocore, MD PhD
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