QIBA Perfusion, Diffusion, & Flow MRI Technical Committee: Current Status

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Brief Summary of Activities in 2012

The RSNA QIBA Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI) Technical Committee expanded its scope during 2012. As a result, the name of the committee was changed to the Perfusion, Diffusion, and Flow MRI Technical Committee (PDF-MRI) and additional members were added to reflect the expansion in scope.

During 2012, the PDF-MRI Technical Committee focused primarily upon: 1) completion of the Phase I DCE-MRI projects (Digital Reference Object, QIBA DCE-MRI Phantom, Phantom Data Analysis Software), 2) release of the DCE-MRI Profile (http://rsna.org/QIBA_.aspx), 3) finalization and activation of a test-retest clinical trial (a Phase II project), 4) initiation of a new Diffusion Weighted MRI Profile, and 5) development of additional groundwork projects needed to expand the initial DCE-MRI Profile to address 3.0T field strength and parallel imaging issues. Details of these initiatives can be found using the PDF-MRI Technical Committee link at http://qibawiki.rsna.org/.

DCE-MRI Profile v1.0

Version 1.0 of the DCE-MRI Profile was released in "public comments addressed" phase following review and approval by the RSNA QIBA Steering Committee. The profile is posted at http://rsna.org/QIBA_.aspx and addresses the following claim: **Quantitative imaging biomarkers reflecting microvascular properties, specifically transfer constant (K^{trans}) and blood normalized initial area under the gadolinium concentration curve ($IAUGC_{BN}$), can be measured from DCE-MRI data obtained at 1.5T using low molecular weight extracellular gadolinium-based contrast agents with a 20% within-subject coefficient of variation for solid tumors at least 2 cm in diameter.**

DCE-MRI Project Summaries

The original focus of our technical committee was to develop the now published Profile, provide tools (phantoms, test guidance, analysis tools) to allow users to implement and comply with the Profile recommendations, and to "field test" the Profile in a clinical trial setting. The deliverables associated with these goals are summarized in the remaining sections. The figure below defines the individual projects, goals, and principal investigators.

Machine Qualification & QC
1.Phantom Development and Testing (Jackson)
2.Software for Phantom Analysis (Ashton)

DCE-MRI Software Evaluation
Digital Reference Object Development (Barboriak)

Clinical Evaluation
Human Trial of DCE-MRI Repeatability (Rosen)

Phase I Funded Project: Machine Qualification and QC

Two projects supported by Phase I QIBA funding were focused upon the development of a commercialized RSNA QIBA DCE-MRI Phantom and associated acquisition protocol and analysis software. The DCE-MRI Phantom design was based on a prototype that was presented in the RSNA QIBA DCE-MRI Technical Committee poster at RSNA 2010. The phantom (Fig. 1) consists of a 36-cm diameter x 15-cm right cylindrical polycarbonate shell filled with a 30 mM NaCl solution and containing two rings of 3-cm diameter spheres filled with $NiCl_2$-doped water. The inner ring of 8 spheres mimics the range of T_1 relaxation rates, R_1, observed for a DCE-MRI vascular input function (VIF), *i.e.*, ~1 - 42 s^{-1}. The outer ring consists of 3 sets of 8 spheres, each with an R_1 range of ~1 – 8 s^{-1} and each set of 8 offset from the previous set by 105º to allow assessment of the impact of surface coil sensitivity effects and the robustness of intensity correction algorithms.

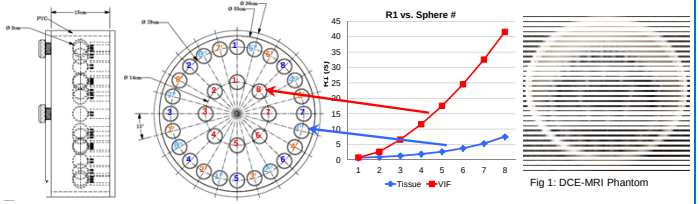

Fig 1: DCE-MRI Phantom

A total of 8 copies of the phantom, without filling solutions, were manufactured by The Phantom Laboratory (Salem, NY). The phantoms were filled with $NiCl_2$ solutions prepared at MD Anderson Cancer Center and the R_1 relaxation rate for each compartment was verified using an inversion recovery imaging sequence. Each phantom was additionally characterized using the acquisition protocol defined below.

A DCE-MRI acquisition protocol was developed and consisted of: 1) a body coil receive fast spoiled gradient echo scan, 2) a phased array receive scan matched otherwise to 1), 3) a variable flip angle (VFA) fast spoiled gradient echo scan, and 4) a DCE-MRI scan. Optional variable TI (inversion recovery) and variable TR (saturation recovery) protocols were also developed. Specific acquisition parameters were established for scanners from GE, Philips, and Siemens.

To provide a standardized data analysis environment, a second phantom-related contract was issued to VirtualScopics, Inc. to develop a Windows-based application that can 1) read each of the series listed above, 2) create a low resolution intensity correction map based on the ratio of the body coil and phased array coil images, 3) automatically define 2-cm diameter ROIs in each of the 32 8-cm spheres, 4) compute T_1 relaxation times and goodness of fit measures from each ROI (for VFA, VTI, and VTR input data) with and without intensity correction using the computed ratio map, 5) compute the SNR and signal intensity vs. time measures from each of the 32 ROIs, with and without intensity correction. The output of the application is a series of text files. These text files then serve as input for an Excel workbook that graphs the results and calculates the following: a) correlation coefficient and Bland-Altman limits of agreement for measured R_1 values (using each technique) *vs.* the known R_1 values, b) the signal intensity change *vs.* known R_1 values in the DCE-MRI acquisition (signal linearity), and c) the coefficient of variation of the mean for each of the ROIs in the DCE-MRI acquisition (signal stability). An example of the phantom data analysis software interface and output results form the Excel workbook are provided in Fig. 2.

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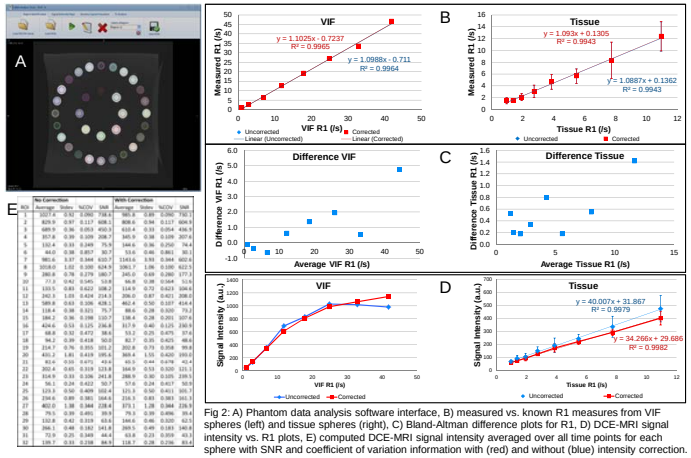


Fig 2: A) Phantom data analysis software interface, B) measured vs. known R1 measures from VIF spheres (left) and tissue spheres (right), C) Bland-Altman difference plots for R1, D) DCE-MRI signal intensity vs. R1 plots. E) computed DCE-MRI signal intensity averaged over all time points for each sphere with SNR and coefficient of variation information with (red) and without (blue) intensity correction.

Phase I Funded Project: DCE-MRI Software Evaluation

Rationale for Digital Reference Object Project

One possible source of bias and/or variance in the calculation of quantitative imaging biomarker measures, such as K^{trans} from DCE-MRI experiments, is the choice of software used to determine intermediate measures used in the calculations, *e.g.*, $1/T_1$ (R_1, the transverse relaxation rate), and/or used to calculate the final measures themselves. The bias and variance accounted for by the software used in the image processing have not been well studied.

In this project, standard MR physics models were used to generate synthetic images called digital reference objects (DROs) for use as test input for a variety of software package. By comparing software outputs in response to identical ground truth input images, the contribution of choice of software to bias and variance can be estimated.

Although DROs vary in important ways from actual imaging data obtained on patients, one advantage of DROs is that known values of underlying parameters are used to create the images. The parameters derived by software packages can be compared with these "ground truth" parameter values, allowing both bias and variance to be evaluated for each software package.

One purpose of the DRO project is to aid in software development in the development / pre-release phase. In addition, the software evaluation process developed in this project is a preliminary step toward the goal of developing reasonable compliance criteria, per the QIBA framework, for software packages used in clinical trials of DCE-MRI. DROs designed to test extreme values of parameter space can be used to gain insight about the conditions under which estimation of model parameters fails for a particular software package. This approach can be helpful to gain insight into the "operating characteristics" of various software packages and acquisition schemes, *e.g.*, the likelihood that a DCE-MRI experiment might reliably detect small changes in K^{trans} at extreme values of noise.

The DROs used in this project are designed to be "open source" objects. Open source software used to generate signal intensities from underlying parameters include JSim (http://physiome.org/jsim/) and ImageJ (http://rsb.info.nih.gov/ij/). Links to these software packages, the models used to generate the DROs, and the DROs themselves are provided on Dr. Barboriak's lab website (https://dblab.duhs.duke.edu/modules/QIBAcontent/index.php?id=1). The DROs are provided both as DICOM images and well as .xml files which can be edited with a text editor and converted into DICOM images using freely available utilities.

Testing of T_1 mapping software packages

As a first step in software package evaluation, a formal evaluation of a variety of academic, open source and commercial software packages used to create T1 maps from variable flip angle MR imaging began in February 2012.

Software outputs from processing of T_1 mapping DROs (QIBA_v1_T1 mapping and QIBA_v3_T1 mapping) have been obtained from 12 software packages and/or package variants. These DROs simulated the extraction of T_1 or R_1 and equilibrium magnetization (S_0) from T_1-weighted spoiled gradient recalled echo or fast low angle shot images with flip angles of 3, 6, 9, 15, 24 and 35 degrees, TR = 5 msec. The range of parameters tested was R_1 values of 0.354, 0.500, 0.707, 1.00, 1.41, 2.00, 2.83, 4.00, 5.66, 8.00, 11.3, 16.0, 22.6, 32.0, and 45.3 s^{-1} and S_0 values of 500, 1000, 2000, 5000, 10000, 20000, 50000. Image sets with superimposed simulated Rician noise were used to study the effect of image noise on parameter extraction and to compare variability of results across software packages. Figure 1 demonstrates example analyses of parameter maps obtained from two software packages using T_1 mapping DROs with no noise added. This analysis shows the effect of varying S_0 and R_1 on bias.

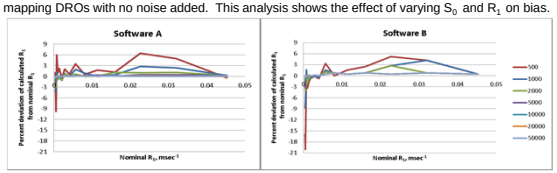


Fig 3. Variation in bias of R_1 parameter derivation for two submitted software packages. Results from identical noise-free input data, each line represents a separate simulated S_0. Both software packages demonstrated less than 3% bias (expressed as deviation of calculated R_1 from nominal R_1 as a percent of nominal R_1) for the vast majority of parameters tested. (Note that for both software packages S_0 lines above 10,000 superimpose with 50,000 line). Except at very low R_1, both packages showed overestimation of R_1.

Comparative Performance Report

Cooperation with industrial and academic partners is an important component of the QIBA alliance. Accordingly, an effort to provide feedback about comparative performance of software was undertaken with the support of the Princeton Internship program of the American College of Radiology Imaging Network. A standardized report is currently in the late stages of development; an example comparative performance parameter is illustrated in the figure below

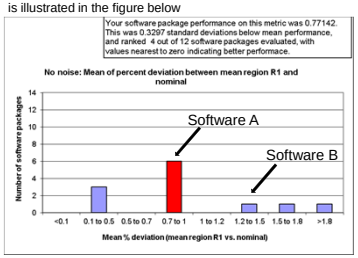


Fig. 4. Example entry in comparative performance report, showing relative performance of software packages in bias for noise-free data. Bias expressed as mean of magnitude of percent deviation between mean calculated R1 and nominal R1 across all tested conditions for noise-free data. Performance categories are listed on the x-axis, with better performance on the left. This example entry was automatically generated from results of submitted packages to provide feedback for developers of Software A. For reference, superimposed arrows indicate relative performance of software A relative to software B for this example.

Phase II Funded Project: Clinical Evaluation

Protocol Concept

In 2011, approval was given by the QIBA steering committee for a test-retest examination of DCE-MRI in human subjects. The project was developed by Mark Rosen, MD, PhD and was co-sponsored by the American College of Radiology Imaging Network (ACRIN, now ECOG-ACRIN). Candidate target populations for this clinical trial were considered. These included the following patient groups:

- Diffuse metastatic disease (abdomen and pelvis)
- Glioblastoma
- Hepatocellular carcinoma
- Locally advanced breast cancer
- Locally advanced cervical cancer
- Prostate cancer

After consultation with the QIBA PDF-MRI Technical Committee, as well as constituent groups in ACRIN, a decision was made to pursue a trial in prostate cancer patients. This decision was based on a variety of considerations, including:

- Access to patients normally presenting for MRI evaluation.
- Ability to incorporate DCE-MRI into routine clinical imaging evaluation.
- Standardization of the treatment status of the patient cohort.
- Presence of competing ACRIN trials.
- Evolving role for quantitative DCE-MRI in both diagnostics and response evaluation

For the selection of some specific technical parameters, it was necessary to weigh the needs of the prostate cancer patient target group against the imaging protocol consensus recommendations reflected in the QIBA DCE-MRI Profile v1.0 while remaining within the general confines of the Profile recommendations. The choices made are summarized below.

Technical acquisition parameter	QIBA DCE-MRI profile	Clinical standard	Test-retest protocol
Magnet strength	1.5T	1.5T or 3T (3T only w/o e-Coil)	3T
Coil	Phased array only	Phase array plus e-Coil	Phase array only
Imaging plane	Coronal	Axial	Axial
Arterial inflow avoidance	Use coronal slab	None	Enlarge axial slab

Protocol Endpoints

Recognizing the importance of diffusion imaging as an emerging quantitative MR biomarker in cancer imaging, the protocol team added diffusion weighted imaging (DWI) as an additional metric of testing. Final protocol objectives are summarized below:

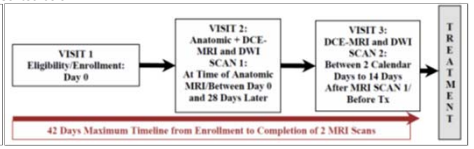
- Determine the test-retest repeatability of the first order gadolinium transfer constant (K^{trans}) and the blood normalized initial area-under the gadolinium concentration ($IAUGC90_{bn}$) evaluation of the whole prostate and dominant prostate tumor nodule.
- Determine the repeatability of the apparent diffusion constant (ADC) of whole prostate and the dominant tumor nodule.
- Determine the relative repeatabilities of DCE-MRI metrics between the T1-dependent (gadolinium-concentration estimate) and the T1-independent (linear approximation method).
- Determine whether the "coffee-break" approach toward test-retest evaluation of DWI offers similar estimate of ADC repeatability compared to the test-retest evaluation performed on different days.

Protocol Schema

The protocol schema is presented below

Inclusion criteria:
- Recent PCA diagnosis
- >minimal tumor burden

Enrollment plan:
- 30 subjects
- 6 sites
- 10 subjects per imaging system vendor



Site qualification

- Requires access to 3T MRI scanner with power injection.
- Minimum 50 prostate MRI cases per year performed.
- Dedicated body MRI radiologist
- Scanner qualification with DWI and DCE-MRI phantom

Time Line

- June 2011: QIBA funding approval
- November 2011: Protocol concept approved by CTEP
- March 2012: Protocol approved by CTEP
- August 2012: First site qualification (per QIBA Profile)
- Sept. 2012: Protocol amendment #1 approved by CTEP