Technical Note

Diffusion Coefficient Measurement Using a Temperature-Controlled Fluid for Quality Control in Multicenter Studies

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Purpose: To present the use of a quality control ice-water phantom for diffusion-weighted magnetic resonance imaging (DW-MRI). DW-MRI has emerged as an important cancer imaging biomarker candidate for diagnosis and early treatment response assessment. Validating imaging biomarkers through multicenter trials requires calibration and performance testing across sites.

Materials and Methods: The phantom consisted of a center tube filled with distilled water surrounded by ice water. Following preparation of the phantom, ≈30 minutes was allowed to reach thermal equilibrium. DW-MRI data were collected at seven institutions, 20 MRI scanners from three vendors, and two field strengths (1.5 and 3T). The phantom was also scanned on a single system on 16 different days over a 25-day period. All data were transferred to a central processing site at the University of Michigan for analysis.

Results: Results revealed that the variation of measured apparent diffusion coefficient (ADC) values between all systems tested was ±5%, indicating excellent agreement between systems. Reproducibility of a single system over a 25-day period was also found to be within ±5% ADC values. Overall, the use of an ice-water phantom for assessment of ADC was found to be a reasonable candidate for use in multicenter trials.

Conclusion: The ice-water phantom described here is a practical and universal approach to validate the accuracy of ADC measurements with ever changing MRI sequence and hardware design and can be readily implemented in multicenter clinical trial designs.

Key Words: diffusion; MRI; phantom; ice water; quality control
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DEVELOPMENT OF NEW quantitative imaging methods for cancer diagnostic and treatment response assessment is under active investigation. The apparent diffusion coefficient (ADC), sensitive to tumor cellularity and response to cytotoxic therapy, is an imaging biomarker under active evaluation. While the basic biophysical premise and technical feasibility of these quantitative imaging approaches are well established, several important practical issues must be addressed prior to routine use in clinical trials. Many of these issues were enumerated in a recent consensus article on use of diffusion-weighted magnetic resonance imaging (DW-MRI) as a cancer biomarker (1). Particularly relevant to the present article are recognized needs to: 1) standardize DW-MRI acquisition schemes across multiple vendors, software, and hardware platforms; 2) develop phantoms to confirm quantitative agreement across platforms; and 3) certify proper calibration and performance of systems at participating multicenter trial sites. Phantoms are often developed for one of two distinct purposes: to reasonably mimic specific tissue properties or serve as a device to test performance of the imaging system. Diffusion in biological systems is complex, as it involves water movement within and among cellular and subcellular elements consisting of macromolecular structures, tortuosity of the extracellular space, and anisotropy of cytoarchitecture. Nondiffusion-related motions from blood flow and bulk tissue motion further complicate in vivo ADC measurement. As a result, it is difficult to develop a stable phantom that truly mimics all tissue properties; thus, some phantoms have been designed to emulate tissue anisotropy (2,3) or multiexponential decay properties (4,5). In terms of phantoms to confirm

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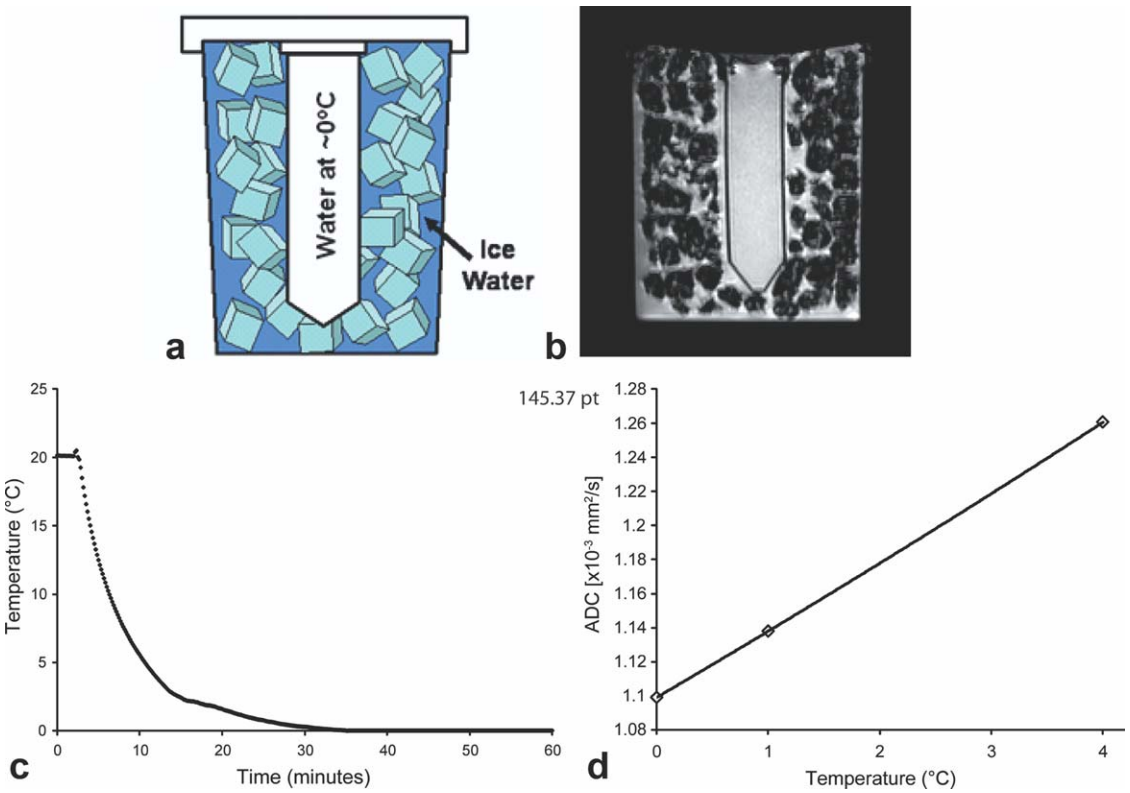

Figure 1. (a) Schematic and **(b)** axial MR image of the ice-water phantom. **(c)** Water in the conical tube was found to reach thermal equilibrium within 30 minutes of placement in the ice-water jacket. **(d)** The dependence of the self-diffusion of water to temperature based on Holz et al (11), with a reported value of $\approx 1.1 \times 10^{-3}$mm^2/s at 0°C.

accurate quantification of diffusion values by MRI systems, simple fluid-based test objects are preferred (1,6). Tofts et al (7) characterized relaxation and diffusion properties of 15 liquids (cyclic alkanes, n-alkanes, and n-alcohols) as a function of temperature (15–30°C). These materials were shown to have diffusion coefficients in the relevant tissue range ($0.36–2.2 \times 10^{-3}$mm^2/s); are stable, readily available, and safe when proper handling precautions are taken. For optimal accuracy in diffusion determination, the temperature of a fluid needs to be determined and controlled as diffusion coefficients are known to vary by 1.7%–3.2%/°C near room temperature (8,9).

The objective of this article is to demonstrate the use of ice water as a universal standard in an ADC phantom developed to address these needs. Once thermal equilibrium is achieved, the ice-water-based alternative proposed herein offers inherent thermal control over an extended interval (several hours) to test/calibrate one or multiple MR systems. Additional favorable properties include safe handling, nontoxic fluid disposal, and low cost. While ice water presents only a single diffusion coefficient, its value is comparable to edematous and tumor tissues thus it offers a reasonable tissue-like b-value-dependent DW-MRI signal decay property.

MATERIALS AND METHODS

Phantom Design

The phantom was constructed from standard labware components: a 50-mL polypropylene conical tube (30 × 115 mm) and 1000-mL polypropylene wide-mouth jar. The 50-mL tube was filled with distilled water, capped, and cemented to the underside of the 1000 mL jar top. Prior to diffusion measurements, cubed or crushed ice and water were added such that ice filled the full extent of the jar. By screwing on the jar top, the 50-mL tube of water was held in the center ice-water mixture. The phantom was wrapped in a hospital "blue pad" for insulation and to absorb surface condensate. Figure 1 illustrates the phantom (Fig. 1a), its suggested positioning for scanning and a representative T1-weighted image through the center of the phantom (Fig. 1b).

Separate from the MRI experiment, a thermocouple was inserted into the conical tube for determination of the time required to reach thermal equilibration between the water in the conical tube and the surrounding ice bath starting from room temperature.

MRI Systems Tested

A total of eight phantoms were constructed with the 50-mL tube filled and cemented in place prior to shipment. Two phantoms were retained for use on multiple systems at the University of Michigan (Ann Arbor, MI) and the remaining were shipped to five additional sites, including the National Institutes of Health (Bethesda, MD), University of Massachusetts (Worcester, MA), Mount Vernon Hospital (Northwood, UK), Royal Marsden Hospital (Sutton, UK), William Beaumont

Table 1
Variability in sequence parameters

Sequence Parameters	Mean	SD
FOV (cm)	23.9	2.4
Number of Slices	16.9	6.1
TR (ms)	4349	2000
TE (ms)	87.1	32.6

Hospital (Royal Oak, MI). These six institutions provided data from 20 different human MRI scanners from three vendors (General Electric, Waukesha, WI; Philips, Best, Netherlands; and Siemens, Erlangen, Germany) and two field strengths (1.5T and 3T). In this study vendors were denoted as Vendors A, B, and C to maintain deidentification of data; thus, attribution of specific data to a specific vendor is not provided. Key attributes for each scanner are provided in Table 1. In addition, to assess single-system repeatability, the ice-water phantom was scanned on one system on 16 separate days over a 25-day interval.

Diffusion-Weighted Image Acquisition

The primary objective was to demonstrate suitability of the ADC ice-water phantom for multiinstitutional trials, with a secondary aim to demonstrate its transportability for obtaining data of agreement in ADC values across different MRI vendors (varying software and hardware platforms), field strengths, and institutions. Rather than detail the specification of acquisition parameters, which can be difficult across vendors and platforms, each center was requested to perform their "local-standard adult brain three-axis DWI protocol," as well as DWI scans at b = 0, 500, 800, 1000, and 2000 s/mm^2. Slice thickness, quantity of slices, acquisition and reconstruction matrix, receiver bandwidth, number of averages, use of parallel imaging, repetition time (TR), and echo time (TE) were *not* specified. The simple nature of this diffusion phantom suggests the measured ADC *should* be independent of these acquisition parameters (including b-value) as long as there is adequate signal-to-noise and low artifact to avoid bias. All acquisition parameters were held constant for the single-system repeatability study.

Diffusion-Weighted Image Analysis

Image data from each system were transferred in DICOM format to the University of Michigan for generation of ADC maps using customized software routines developed in MatLab (MathWorks, Natick, MA). ADC maps were calculated from low b = 0 images (S_0) and high b (S_b) image pairs according to:

$$ADC_b = \frac{1}{b}\ln\left[\frac{S_o}{S_b}\right], \quad [1]$$

where high b = 500, 800, 1000, and 2000 s/mm^2. That is, four sets of ADC maps were generated for each scanner: ADC_{500}, ADC_{800}, ADC_{1000}, and ADC_{2000}. A rectangular region-of-interest (ROI) of area 360 ± 30 mm^2 was manually defined on ADC maps on the central slice through the 50-mL tube and ROI mean and standard deviation were recorded.

Statistical Analysis

Of the 20 scanners, 12 were 1.5T and 8 were 3T. Due to the small number of 3T systems from Vendors A and C, comparison of ADC measurements by field strength or vendor was performed on pooled data. An analysis of variance (ANOVA) was used to assess the differences in ADC values measured at each b-value between magnetic field strengths, vendors pooled, and vendors, field strengths pooled. Differences in ADC measurements obtained using b-values of 500, 800, 1000, and 2000 s/mm^2 were assessed separately for each vendor, pooling data from both field strengths, by repeated measures (rm)-ANOVA. Multiple comparisons of the main effect were adjusted using a Bonferroni post-hoc test. For the single-system repeatability study normality of ADC measurements at each b-value was determined using a one-sample Kolmogorov–Smirnov test. A one-sample *t*-test was performed to determine differences of ADC values at each b-value from the literature value of $\approx 1.1 \times 10^{-3}$ mm^2/s (8–10). Finally, differences in ADC values acquired at different b-values were assessed as described for vendor comparisons. Statistical significance was assessed at $P < 0.05$. Data are presented as the mean ± SD.

RESULTS

As depicted in Fig. 1c, upon inserting the tube of room temperature water into ice-water jacket, ≈30 minutes was required for the central fluid to reach an equilibrium temperature of ≈0°C. Water maintained at 0°C has a literature ADC value of $\approx 1.1 \times 10^{-3}$ mm^2/s (Fig. 1d) (8–11). Water within the tube was easily delineated from the ice bath by MRI as a result of the lack of signal intensity from the tube wall (wall thickness ≈1 mm). This provided ease of prescribing an ROI within the tube. The high sensitivity of water diffusion with temperature makes it important to have a stable temperature over long periods of time. As reported from various sources in the literature and shown in Fig. 1d, water ADC increases at a rate of 2.4%/°C (8,9). We have found that our ice-water phantom was capable of maintaining a temperature ≈0°C for up to 3–4 hours (data not shown). This provides the thermal stability necessary for acquiring ADC measurements on multiple systems using the same preparation over this period.

The objective of this study was not to propose a set of sequence parameters for acquiring an ADC measurement of ice water, but to determine the accuracy of these measurements using an ice-water phantom over a variety of vendor instruments using site-specific protocols for acquiring ADC measurements of the human brain. As presented in Table 1, a wide variety of basic sequence parameter settings were used by different sites to acquire the DW-MRI data. TR and TE

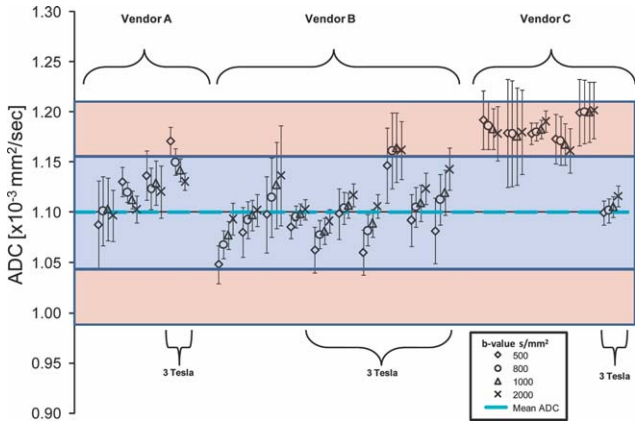

Figure 2. Measurements of the ADC of the ice-water phantom separated by site, vendor, magnetic field strength, and b-values.

were found to be highly variable between sites, ranging from 1000–8000 msec and 51–167 msec, respectively.

Irrespective of the variability in sequence parameters between sites, we found that ADC measurements of the ice-water phantom were consistent with the literature value for water at ≈0°C (8–10). Presented in Fig. 2 are the grouped ADC values, acquired at b-values of 500, 800, 1000, and 2000 s/mm^2, from the ice-water phantom for each individual system ($n = 20$). A total of 80 measurements were obtained and 86% of the values were within 5% (blue field in Fig. 2) of the literature value of 1.1×10^{-3} mm^2/s (10). All measurements were within 10% (denoted by red fields in Fig. 2) of this value. ADC values acquired using Vendor C systems at 1.5T were noticeably higher than the sole 3T system from the same manufacturer. Nevertheless, magnet field strength, when pooled over all systems, was not found to have an impact on ADC measurements. In contrast, differences in ADC were observed between system manufacturers. Vendor C, driven heavily by the 1.5T systems, had a significantly higher ADC measurement than Vendors A and B, when acquired using b-values of 800 ($P = 0.02$ and $P < 0.0001$), 1000 ($P = 0.01$ and $P < 0.0001$), and 2000 ($P = 0.002$ and $P = 0.001$) s/mm^2. At a b-value of 500 s/mm^2 Vendor B was found to have a significantly lower ADC value than both Vendors A ($P = 0.02$) and C ($P < 0.0001$). In general, all systems manufactured by Vendor B produced ADCs that increased with increasing b-values, with differences in ADC values observed between all b-value combinations ($P < 0.01$). Vendor A produced ADC values that differed when acquired using b-values of 1000 and 2000s/mm^2 ($P = 0.02$), whereas no statistical difference in ADC with b-value was observed for Vendor C.

The single-system repeatability study using a Vendor B-manufactured system showed a steady increase in ADC values for increasing b-values at each examination (Fig. 3). Nevertheless, a mean ADC of 1.09×10^{-3}mm^2/s was obtained using all measurements. At individual b-values, ADCs (mean ± SD) were 1.07 ± 0.02, 1.09 ± 0.02, 1.09 ± 0.02, and 1.1 ± 0.02 $\times 10^{-3}$mm^2/s acquired at 500, 800, 1000, and 2000 s/mm^2, respectively. These measurements were not found to deviate from normality. When comparing these ADC values to a test value of 1.1×10^{-3}mm^2/s, only measurements obtained with b-values of 500 and 800 s/mm^2 deviated significantly from the test value ($P < 0.0001$ and $P = 0.02$, respectively). All combinations of b-values resulted in significantly different ADC values.

DISCUSSION

DW-MRI, a standard sequence on most MRI systems, has found widespread use for diagnostic and prognostic applications in the medical community (1,12–15). The attractiveness of this technique is its high sensitivity to microenvironmental changes in living tissue that commonly occurs upon the onset or treatment of disease. In addition, this MRI technique is inherently noninvasive, requiring no contrast administration. Although widely used, there remains little conformity in the "preferred" diffusion MRI hardware, sequence, and parameters, with scan protocols defined differently between vendors and sites. We sought to determine the reproducibility of the diffusion measurements across clinical platforms and sites by employing a universal, temperature-controlled fluid. The diffusion sequences were locally defined for brain imaging using parameters and hardware specific to each individual site. No request was made to modify the standard operating procedure, only that they follow the setup procedure for measuring ADC using the ice-water phantom.

The physical properties of water are well characterized in the literature, making it a good candidate for diffusion measurements by MRI (8–10,16). Unlike some other proposed fluids, water is inert, making it free of special handling requirements, and is readily available (7). A limitation in using any fluid where viscosity and molecular mobility vary with temperature is the need for temperature determination and control. To circumvent this limitation, liquid water was jacketed within ice water and allowed to equilibrate. This not only sets the test fluid to a known temperature, but also

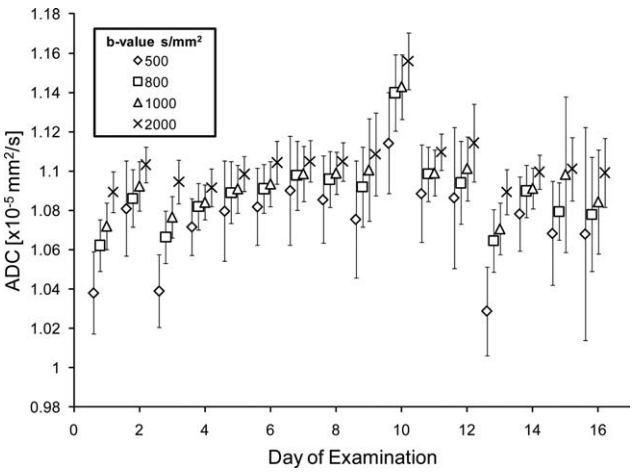

Figure 3. Repeatability in the measurements of the ADC of the ice-water phantom acquired at different b-values was performed at a single site on 16 different occasions over a 25-day period.

maintains that temperature as long as sufficient ice remains in phase transition to water. We found that ≈30 minutes was required for the liquid water to reach a temperature ≈0°C (Fig. 1c) and that this temperature was maintained for several hours.

As expected, there were site-specific variations in MR hardware and sequence parameters (Table 1), with repetition and echo times varying quite substantially. Despite these variables, the large majority of ADC values were within 5% of literature values, with all 80 measurements within 10%. These variations were in agreement with the work performed by Sasaki et al (17), who, using healthy subjects, demonstrated the variability in absolute ADC of white and gray matter in brain tissue across different platforms. For their study, sequence parameters were attempted to be as consistent as possible. Sasaki et al report intervendor variability up to 7% and intravariability up to 8%. ADC values fluctuated by up to 5% when the same volunteers were imaged on the same scanner. Use of our ice-water phantom across vendors and multiple examinations on the same scanner are consistent with their results, despite not setting controls on site sequence parameters. In addition, we observed ADC variability at different b-values. Based on first principles, ADC of water should not have a b-value dependence. Nevertheless, Vendor B systems were found to steadily increase ADC with increasing b-value. This effect was small (<5%) but significant and may be a result of eddy-current effects resulting in the true b-value being slightly higher than the assumed b-value. Detection of such small effects could not be easily performed on living tissue (ie, brain), due to nonmonoexponential trends in DW signal attenuation typically observed in biological systems (2,15,18,19).

In conclusion, the extensive use of the absolute ADC as a predictive surrogate biomarker of disease and treatment-induced response has made validation and calibration of individual systems a prerequisite for quality control (1,12–15). With advances in rapid imaging techniques, DW sequences and radiofrequency coil design, conformity to a predescribed DWI protocol is difficult to achieve across multiple sites and system platforms. Requiring only inexpensive material that is readily available and 30 minutes to reach thermal equilibrium, the proposed ice-water phantom is a practical and universal approach to validating the accuracy of ADC measurements with ever-changing MRI sequence and hardware design.

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