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# Deuterium nuclear magnetic resonance measurements of blood flow and tissue perfusion employing $^2H_2O$ as a freely diffusible tracer

**(rat liver/surface coil/spin-lattice relaxation/heavy water)**

JOSEPH J. H. ACKERMAN*†, COLEEN S. EWY*, NANCY N. BECKER*, AND ROBERT A. SHALWITZ†‡

‡Department of Pediatrics, Washington University School of Medicine, St. Louis, MO 63110; and *Department of Chemistry, Washington University, St. Louis, MO 63130

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**ABSTRACT** **The use of deuterium oxide ($^2H_2O$) is proposed as a freely diffusible nuclear magnetic resonance (NMR) blood flow and tissue perfusion tracer of potential clinical utility. Deuterium is a stable, nonradiative isotope commercially available as $^2H_2O$ at enrichment levels of essentially 100%—i.e., 110 molar equivalent deuterium. This high concentration, together with the short relaxation time of the spin 1 (quadrupole) deuterium nuclide, provides substantial sensitivity for NMR spectroscopy. As a result, when $^2H_2O$ is administered in a bolus fashion to a specific tissue or organ *in vivo*, the deuterium NMR intensity time course can be analyzed, using mathematical models developed by others for radiolabeled tracers, to measure the rate of blood flow and tissue perfusion. Such an application is demonstrated herein at a static magnetic field of 8.5 tesla. Using single-compartment flow modeling, hepatic blood flow and tissue perfusion in fasted (18 hr) male Sprague–Dawley rats was determined to be 61 ± 17 (mean ± SD) ml/100 g per min ($n$ = 5).**

The measurement of regional blood flow and tissue perfusion provides an important clinical indicator of tissue viability and vascular competency. Nuclear magnetic resonance (NMR) flow measurement techniques, including those based on spin-imaging procedures, that employ observation of the naturally abundant $^1H$ resonance from $H_2O$ have been developed (for reviews, see refs. 1–3). These techniques generally rely on the spatial evolution of $^1H$ magnetization after the initial preparation of a nonequilibrium spin-state population distribution. Therefore, magnetic resonance flow measurements are often limited by the lifetime of the nonequilibrium state and, thus, by the water spin-lattice and spin-spin $^1H$ relaxation times. However, such approaches are extremely attractive because of their completely noninvasive nature and their development remains an area of very active investigation (4, 5).

Alternatively, as described in the early pioneering work of Kety (6–8), one can introduce an exogenous substance as a blood-flow tracer, usually one containing a radiolabel. Although the administration of the tracer substance introduces an invasive character to the flow measurement, the high sensitivity of nuclear decay detection and the use of radiolabels that decay slowly relative to blood flow result in measurement methods of considerable practical utility (9–11). Importantly, by employing tracer substances that freely diffuse through aqueous spaces (i.e., intracellular, interstitial), a quantification of tissue perfusion is achieved in contrast to a measurement of simply linear or plug flow velocity in large vessels. One such tracer substance that has seen considerable use in combination with positron emission detection is $H_2{}^{15}O$ (12–18).

We propose herein the analogous use of $^2H_2O$ as a diffusible blood-flow and tissue-perfusion tracer where deuterium NMR is used to monitor label intensity as a function of time. Deuterium is a nonradiative, naturally abundant (0.0156%), quadrupole nuclide with only 0.01 the sensitivity of $^1H$. Nevertheless, the combination of an efficient quadrupole relaxation mechanism and the commercial availability of $^2H_2O$, essentially 100% enriched to *ca.* 110 molar equivalent deuterium, can provide substantial NMR signal-to-noise in the intact subject. This is readily illustrated herein through surface-coil NMR (19, 20) examination of rat liver *in vivo* employing an animal model developed previously in our laboratory. Portions of this study have been presented in abbreviated format (22, §).

## METHODS

Male Sprague–Dawley rats (Sasco, Omaha, NE) were fasted for 18 hr, weighed (*ca.* 225 g), and anesthetized with Halothane (5% for induction, 2% for surgery, 1% for maintenance). Animals remained under anesthesia throughout the entire experimental protocol and were sacrificed at its conclusion. Since magnetic resonance imaging localization techniques were unavailable, spatial localization was achieved surgically in our studies. A 4-cm transverse, subcostal incision was made in the abdomen to expose the liver. The xiphoid process was removed and the falciform ligament was cut. An infusion catheter was secured in a branch of the superior mesenteric vein and kept patent with heparinized saline (0.9% NaCl) infused at 0.013 ml/min. The abdomen was wrapped in plastic wrap to prevent moisture loss and the animal was secured in the cradle of the NMR probe. (Body temperature was maintained at 37°C by warm water circulation.) The probe and animal were then brought to the vertical position and the surface-coil antenna was placed on a 1-mm-thick glass plate positioned over the liver.

Following standard blood-flow measurement protocols (9), the time evolution of the deuterium NMR integrated signal intensity from rat liver *in vivo* was followed with typically 0.51-sec time resolution after bolus injection of 0.2 ml of $^2H_2O$ into a branch of the superior mesenteric vein.

The surface-coil antenna was a coaxial double-coil arrangement similar to that described for *in vivo* $^{13}C\{^1H\}$ experiments (20). An outer 2-cm-diameter coil tuned to 360 MHz was used to observe $^1H$ (i.e., $H_2O$) for optimization of the static field (8.5 tesla) homogeneity while the smaller inner 1-cm-diameter coil was used for deuterium observation at 55 MHz. During the measurement of hepatic blood flow (HBF) and tissue perfusion, data collection and storage were assigned to

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Abbreviation: HBF, hepatic blood flow.

†To whom reprint requests should be addressed.

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computer memory throughout the experiment to avoid disk access timing delays. A nonlinear least squares fitting routine was used to fit the experimental resonance lines to a Lorentzian lineshape (23). From this simulated lineshape function, an analytical (i.e., closed form) determination of the integrated resonance area was obtained.

## RESULTS AND DISCUSSION

The results of a spin-lattice relaxation time ($T_1$) measurement (24) on the naturally abundant deuterium present in hepatic tissue water ($^1H^2HO$) are shown in Fig. 1. Nonlinear least squares analysis in terms of a three-parameter, single-exponential magnetization-recovery time course yields a time constant $T_1$ = 0.25 sec. This relatively short $T_1$ allows rapid signal-to-noise enhancement through pulsed Fourier transform time-averaging techniques (25) and, in combination with a high isotopic enrichment of $^2H_2O$, provides for short time resolution serial monitoring of the deuterium resonance intensity. Fig. 2 illustrates a natural abundance background deuterium signal from rat liver *in vivo* (160 scans summed over 82 sec) and the hepatic signal a few seconds after bolus injection of 0.2 ml of $^2H_2O$ into a branch of the superior mesenteric vein (1 scan). The superior mesenteric vein leads directly into the portal vein through which *ca.* 70% of the hepatic blood supply passes. Clearly, this model system using $^2H_2O$ as a freely diffusible tracer has adequate signal-to-noise and time resolution to demonstrate the measurement of blood flow and tissue perfusion in the intact animal.

Fig. 3 shows that immediately following bolus administration, there is a very rapid marked increase in integrated resonance intensity as the deuterated tracer enters the liver vascular space and diffuses into the tissue. Concurrent rapid proton exchange yields $^1H^2HO$. This is followed by a slow exponential decrease in integrated signal intensity (note the logarithmic ordinate in Fig. 3) indicative of hepatic $^1H^2HO$ washout by ongoing blood flow. No overshoot of integrated signal intensity prior to washout is observed showing that HBF is slow enough to ensure accurate approximation of $^2H_2O$ as a freely diffusible tracer (13).

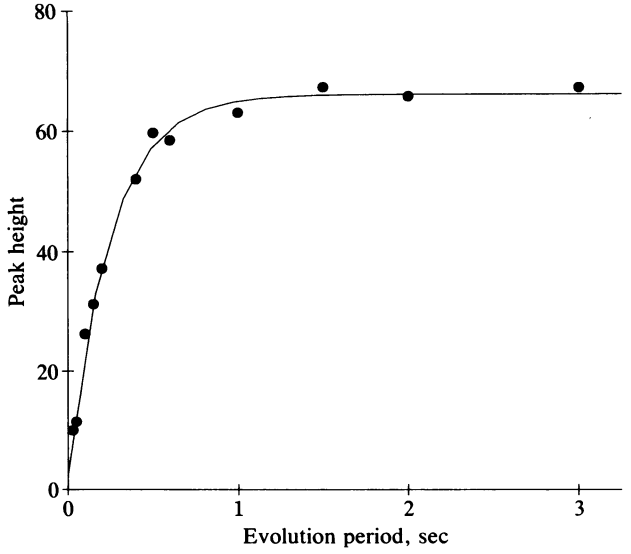


FIG. 1. Magnetization saturation recovery time course (peak height vs. evolution period) obtained during the surface-coil NMR measurement of the naturally abundant hepatic deuterium ($^1H^2HO$) spin-lattice relaxation time ($T_1$) *in vivo* using methodology described by Evelhoch and Ackerman (24). The symbol ● represents the experimental points, whereas the solid curve represents the result of a nonlinear least squares fit of these data to a three-parameter, single-exponential function of the form: $y = A + Be^{-t/T_1}$. Here $T_1$ is the exponential time constant governing the rate of recovery of deuterium magnetization along the axis of the 8.5-tesla static magnetic field. The least squares fit gave a $T_1$ value of 0.25 sec.

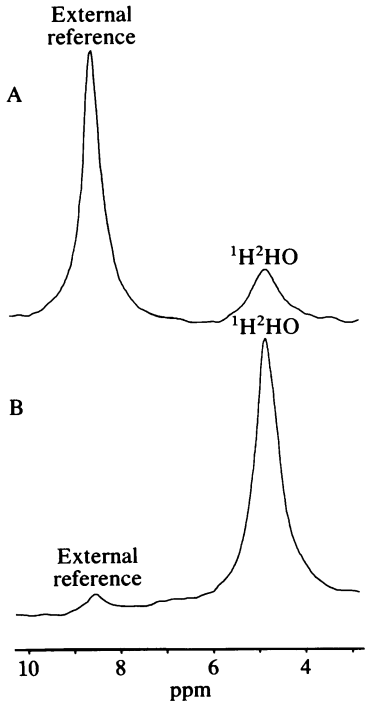


FIG. 2. Representative deuterium spectra from rat liver *in vivo* at 55.28 MHz. (*A*) Natural abundance deuterium spectrum consisting of 160 free induction decays accumulated and summed over 82 sec and Fourier-transformed after application of a 10-Hz exponential filter. The external reference resonance represents a small capillary, positioned between the lobes of the liver, containing $C_6{}^2H_6$ plus chromium acetyl acetonate as a relaxation (and shift) agent. (*B*) Single transformed free induction decay (0.20-sec accumulation) of the same liver as in *A* 4 sec after a bolus injection of 0.2 ml of $^2H_2O$ into a branch of the superior mesenteric vein. A 10-Hz exponential filter was applied prior to Fourier transformation.

Given a one-compartment model (rapid tracer diffusion between vascular and extravascular spaces) and assuming a bolus tracer input (i.e., a pseudo delta function), homogeneous tissue vascularization with no intracompartment tracer concentration gradients, and negligible recirculation of labeled material, an exponential decay of tissue tracer concentration is expected (9–11). The tracer washout *exponential time constant* ($T$) can be related to blood flow per unit volume (or mass) of tissue through the central volume principle of tracer kinetics (10, 11). This leads to an expression for HBF in units of ml/100 g per min as given by Eq. **1**,

$$\text{HBF} = \lambda/T, \qquad [1]$$

where $\lambda$ is the mean equilibrium liver–blood partition coefficient of water. The coefficient $\lambda$ is the ratio of the water weight of a unit mass (100 g) of liver tissue (including vascular spaces) to the water weight of a unit volume of blood. Such water content was determined from the wet and dry weights of liver and blood and the density of blood, 1.06 g/ml. For rat liver, $\lambda$ was determined to be 83.1 ± 0.6 (mean ± SD) ml/100 g ($n$ = 3). Exponential fitting of the data of Fig. 3 results in $T$ = 2.01 min and gives a value of HBF = 41 ml/100 g per min. Inclusion of results from additional animals gave a mean value of 61 ± 17 (mean ± SD) ml/100 g per min ($n$ = 5). This compares favorably with Steiner's determination of HBF in

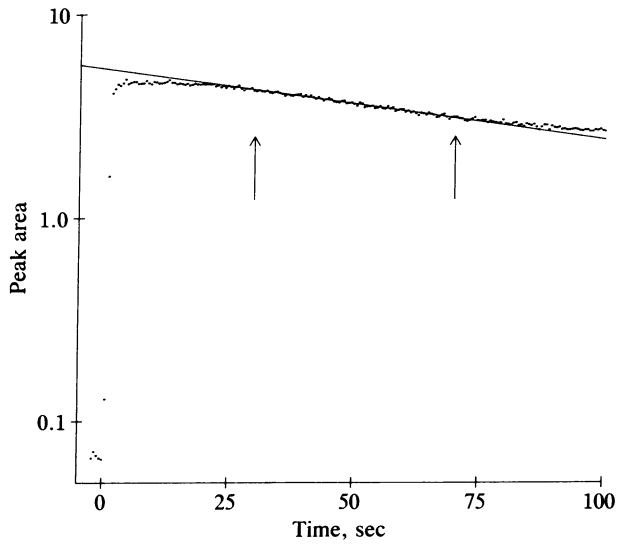


FIG. 3. *Semilogarithmic* plot of the hepatic deuterium integrated resonance intensity time course following a bolus injection of 0.2 ml of $^2H_2O$ into a branch of the superior mesenteric vein of a fasted (18 hr) anesthetized Sprague–Dawley rat. The symbol · represents experimental points, whereas the solid line represents the result of a nonlinear least squares fit of the data between 30 and 70 sec (arrows) to a two-parameter single-exponential of the form: $y = Ae^{-t/T}$. $T$ is the exponential time constant governing the rate of blood-flow washout of the deuterium label from the liver tissue. For the data shown here, $T$ is found to be 2.01 min; this leads to a calculated HBF (using Eq. 1) of 41 ml/100 g per min. The five control period baseline data points taken prior to $^2H_2O$ administration represent 160 scans per point scaled appropriately (i.e., resonance integrated areas were divided by 160) to correspond to single-scan data points. This improved signal-to-noise for these low intensity points by *ca.* 13-fold. The leveling off of the signal intensity time course curve at late time points results from recirculation of deuterium label back into the liver. This represents a breakdown at later time points in one of the assumptions (negligible label recirculation) of the blood-flow measurement model employed here.

the fasted Sprague–Dawley rat, HBF = 80 ± 35 (mean ± SD) ml/100 g per min ($n$ = 17) (26).

Preliminary validation experiments strongly suggest that hydrogen–deuterium exchange between exogenous $^2H_2O$/$^1H^2HO$ label and proton-labile endogenous materials does not markedly compromise the single-compartment flow analysis employed herein. (This is reasonable given the substantial molar excess of tissue water protons relative to sites of potential proton exchange.) For this validation, deuterium NMR surface-coil blood-flow measurements were performed on *ex vivo* perfused rat liver. Here the perfusate volumetric flow rate (ml/min) was accurately measured independently of the NMR determination and a nonrecirculating perfusion medium was used to more closely approximate the single-compartment model by eliminating the problem of tracer reflow observed *in vivo*. Considering eight separate flow determinations, the mean NMR measurement deviation (error) from the actual flow rate was 0.6% ± 8.9% (SD), suggesting considerable precision and a lack of bias toward either an over- or underestimation of the actual flow rate. The mean NMR measurement error *magnitude* was 5.6%.

Since deuterium is a stable, nonradiative isotope it offers procedural advantages in comparison to radiolabels. Nearby cyclotron facilities are not needed and special procedures and laboratory restrictions required in the handling of radioisotopes are not required. Furthermore, $^2H_2O$ appears to be relatively nontoxic except at very high chronic levels (27–47). Therefore, it has potential clinical use in the study of regional blood flow. In this light, it is worth noting in a speculative vein that because of the relatively low cost of $^2H_2O$, *acute* tissue water enrichment to 1–5% $^2H_2O$ appears reasonable and would provide sufficient sensitivity for deuterium NMR spin-imaging. For example, $^{23}Na$ images have been successfully obtained by others (48–51) and, assuming 100% NMR visibility, a 1% $^2H_2O$ labeling of tissue water (1.1 M deuterium) should result in roughly twice the NMR signal intensity as naturally abundant tissue $^{23}Na$ (66% × 10 mM intracellular, 33% × 140 mM extracellular). Presumably, such experiments can be readily carried out with the new generation of multinuclear NMR spectroscopy/imaging systems. Deuterium spin-images of intact biological systems have been obtained recently (52, 53). [Similar approaches with $^{19}F$-labeled tracers may be feasible (55–62).]

Finally, we point out that since deuterium has 0.6 the NMR sensitivity of $^{13}C$ and exhibits short relaxation times, it has potential for use as an *in vivo* chemical shift metabolic tracer in a manner analogous to that employed with $^{13}C$. We have observed, for example, rat hepatic deuterium resonances of substantial intensity and narrow linewidth (*ca.* 20 Hz at 8.5 tesla) *in vivo* following intraduodenal bolus administration of physiological levels of D-glucose-1-$d_1$ or sodium acetate-$d_3$ (experiments with sodium acetate-$d_3$ were performed in colaboration with David Foxall and Brenda Nichols of Varian Instruments, Freemont Division, Freemont, CA). Under conditions of chronic $^2H_2O$ administration, endogenous labeling of various materials can also be observed (21). Natural abundance deuterium NMR has recently been used to determine body iron stores (54).

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