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The measurement of blood flow parameters with deuterium stable isotope MR imaging

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Methods: Because there are no radioactive hydrogen isotopes which can be used for clinical examinations, deuterium as a non-radioactive, freely diffusible tracer has some advantages compared with the radioactive tracers in the measurement of blood flow parameters. A non-invasive technique to estimate the mean tissue blood flow parameter *in vivo* was developed by using deuterium nuclear magnetic resonance (NMR) imaging in rat. We obtained the NMR signal changes from deuterium NMR images in nine male Wister rats after intravenous injection of D_2O and applied exponential curve fitting analyses to calculate blood flow parameters of the brain, heart and skeletal muscle.

Results: While fitting the reducing of the monoexponential function yielded a blood flow parameter of 27.9 ± 1.6 m*l*/min/100 g tissue weight for the brain and 46.7 ± 3.7 m*l*/min/100 g tissue weight for the heart, fitting the early reducing of the signal intensity of the biexponential function yielded a blood flow parameter of 95.6 ± 10.9 m*l*/min/100 g tissue weight for the brain and 108.0 ± 13.1 m*l*/min/100 g tissue weight for the heart. The mean muscle blood flow parameter determined by the monoexponential uptake function was 43.8 ± 7.3 m*l*/min/100 g tissue weight.

Conclusions: The blood flow parameter measurement by means of an imaging coil for deuterium is less invasive and reflects the mean tissue blood flow parameter for the entire tissue sample more homogeneously than spectroscopic monitoring.

Key words: brain, heart, skeletal muscle, blood flow, ^{2}D-MRI

INTRODUCTION

DEUTERIUM as a freely diffusible tracer has been applied to the washout blood flow measurement of tumors,[1] brain[2,3] and other organs[4–6] of experimental animals with nuclear magnetic resonance (NMR) spectroscopic monitoring. The non-radioactive deuterium may have an advantage over radioactive tracers and microspheres in the measurement of blood flow and tissue perfusion. Furthermore, deuterium as a stable isotope is more advantageous than the short-lived radioactive tracers in quantifying very low rates of blood flow (tumor and muscle).[1,7,8] *In vivo* NMR deuterium imaging has also recently been demonstrated in rat and cat brain,[9] providing complementary information about tissue characterization.

In spite of these advantages of deuterium for blood flow measurement, the methods of spectroscopic monitoring have so far been relatively invasive, in requiring intratumoral injection, intracarotid injection, and scalp retraction for the surface coil. Furthermore, the region of tissue measured with the surface coil is considered to be limited to a small and superficial area. The imaging coil for deuterium has never been applied to measure blood flow. We developed a method to measure the blood flow parameter with deuterium NMR imaging, it may have the potential for future clinical application.

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MATERIALS AND METHODS

Animal preparation

Nine male Wister rats (A-1) weighing 330–440 g were

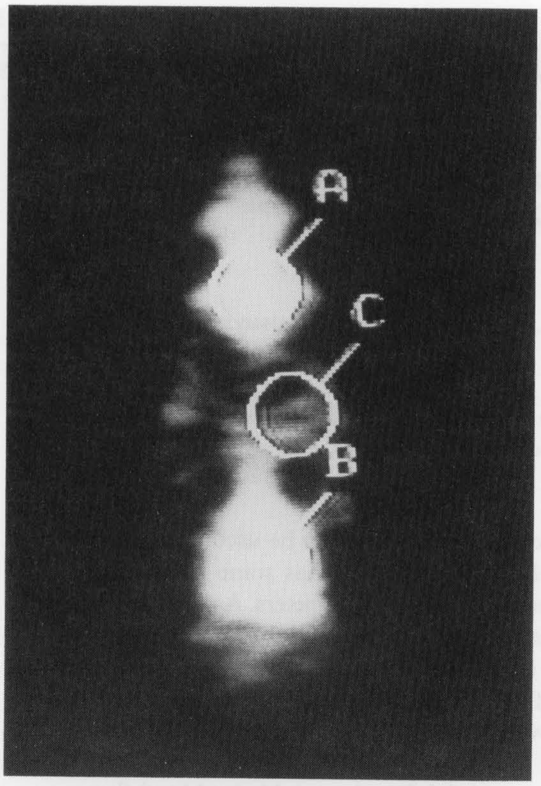

Fig. 1 The heart appears first then the brain and the muscle increases signals gradually. A represents for the region of interest (ROI) for the brain, B for the heart and C for the muscle.

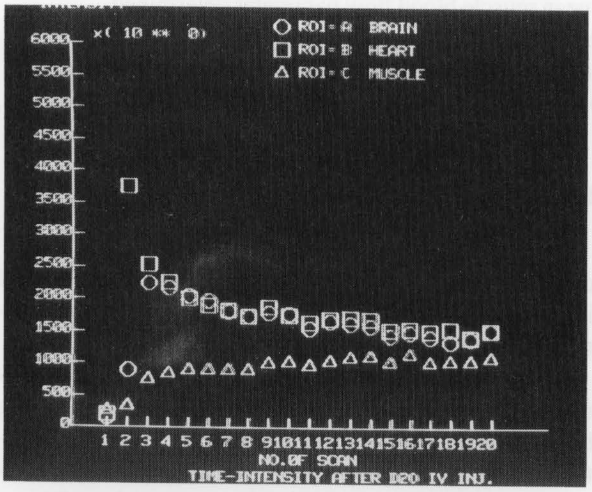

Fig. 2 The time-intensity plots for the brain (○), the heart (□) and the muscle (△) each of which is characteristic for each tissue. Tracer washout decay curve with bi-exponential fitting.

used. The rats were anesthetized with intraperitoneal chloral hydrate. A saline solution was prepared with 99.75% D_2O.

NMR imaging

An anesthetized rat was placed inside a coil, a slotted tube resonator of Alderman-Grant type. The rats received an intravenous (tail vein) bolus injection of deuterated saline (0.83 m*l*/100 g for rats A–E, 0.67 m*l*/100 g for F–I) immediately after the first image was obtained, which was followed by 30 consecutive field echo coronal or sagittal images with a 32 cm field of view, non-selective slice thickness, and 64 × 128 matrix. The pulse sequence induced a repetition time (TR) of 150 msec, an echo time (TE) of 5 msec, and single acquisition, so that about 19 seconds was required for each image. The resonance frequency of deuterium was 13.09 MHz on a 2.0 T magnet system (RS-200; Siemens-Asahi, Tokyo, Japan).

Data analysis

For the brain and the heart, in the two-compartment in-series kinetic model with monoexponential uptake and monoexponential clearance with tracer recirculation, we assume the formula

$$I(t) = (I(0) - I(\infty)) \times (e^{(-k1 \times t)} - e^{(-k2 \times t)}) \quad [1]$$

where I(t) is the signal intensity at time t, so I(0) and I(∞) are signal intensities at the times 0 and ∞, respectively. K1 and k2 are the rate constants governing tracer washout and uptake, respectively. The another biexponential model with two in-parallel washout parameters with tracer recirculation was also applied to the brain and the heart, using the formula

$$I(t) = Ia(0) \times e^{(-ka \times t)} + Ib(0) \times e^{(-kb \times t)} + I(\infty) \quad [2]$$

where I(t) is the signal intensity at time t and $Ia(0) \times e^{(-ka \times t)}$ and $Ib(0) \times e^{(-kb \times t)}$ represent the fast and slow washout curves with rate constants of ka and kb, respectively.

For the muscle the monoexponential uptake is used for fitting with the formula

$$I(t) = I(\infty) - I(\infty) \times e^{(-k \times t)} \quad [3]$$

where k is the rate constant governing tracer uptake.

After subtraction of the background the data were fitted to the formulae [1] and [2] for the brain and the heart and to formula [3] for the muscle by using the nonlinear least-squares method. The volumetric rate blood flow parameters (m*l*/min/100 g tissue) were calculated on the central volume principle by means of the formula

$$\text{blood flow parameter (BFP)} = 100 \times \lambda \times k' \quad [4]$$

where λ is the tissue-to-blood partition coefficient assumed to be $\lambda = 0.75$ and k′ represents the rate constant (k1 from formula [1], ka from formula [2] and k from formula [3]).

RESULTS

For the 20 consecutive images for the brain and the heart and 30 images for muscle, the region of interest (ROI) was applied respectively, to the brain, heart and muscle (Fig. 1).

The characteristic time-intensity curve was obtained for each tissue (Fig. 2). Fitting the early decay of the curve by using formula [1] or [2] yielded the blood flow parameters for the brain and the heart as shown in the Table 1.

Table 1 The blood flow parameters of the brain and the heart using monoexponential and biexponential curve fitting. [ml/min/100 g tissue followed by standard errors]

Tissue	by monoexponential curve fitting	by biexponential curve fitting
Brain	27.9 ± 1.6 (n = 9)	95.6 ± 10.9 (n = 5)
Heart	46.7 ± 3.7 (n = 8)	108.0 ± 13.1 (n = 4)

The mean muscle blood flow parameter determined with formula [3] was 43.8 ± 7.3 m*l*/min/100 g tissue, (n = 4).

DISCUSSION

We measured the blood flow parameter from the consecutive deuterium images with an imaging coil. Mean cerebral blood flow determined by deuterium spectroscopy has been reported as 42 ± 4.2 m*l*/min/100 g tissue in piglet[2] and 70 m*l*/min/100 g tissue in cat,[3] and the cerebral blood flow was reported as 69.9 ± 3.5 m*l*/min/100 g tissue in rat with the hydrogen clearance method,[10] and 135 ± 13 m*l*/min/100 g tissue in rat with the ^{133}Xe clearance study.[11] Our data are close to these previously reported data and seem to be comparable considering that the cerebral blood flow values are vary widely in parallel with $PaCO_2$.[3]

On the other hand, the mean muscle blood flow parameter was greater than that reported previously,[8] probably because our ROI for the muscle might have included vessels, and/or the time course might not have been long enough for the uptake study.

Numerous papers have been published on the biologic effects of deuterium oxide. Deuterium oxide appears to be relatively nontoxic except at high chronic levels.[12–14] In 1986 Brereton et al. applied *in vivo* deuterium NMR spectroscopy for the first time to investigate the D_2O turnover in water and fat in mice.[15] Since his study, *in vivo* deuterium NMR imaging[9] and spectroscopy[1–9,18] have been studied independently. Cerebral blood flow has also been measured by spectroscopic or imaging detection of fluorinated gas.[19] Considering the advantages of deuterium over radiotracers and radioactive microspheres in the measurement of blood flow and tissue perfusion,[7,8] deuterium has a potential clinical use in the study of regional blood flow. Neil emphasized that while the mathematics are more complicated for nonbolus tracer input than for bolus input, the nonbolus input offers the advantage of allowing tracer administration remote from the organ of interest less invasively.[20]

We reported that acute parenteral enrichment of deuterium oxide 1 m*l* per 100 g body weight in rat provides good *in vivo* NMR imaging. Here we showed that an intravenous bolus injection of deuterated saline of 0.63 m*l* per 100 g body weight in rat was good enough to delineate consecutive deuterium images for blood flow parameter measurement. *In vivo* turnover of deuterium is approximately 3 to 4 days[16] in mice and 8 to 10 days in humans. Since D_2O (or more precisely HOD as a result of rapid proton exchange) is not quickly expelled through the lungs, one needs to include the effect of label (HOD) recirculation in the kinetic analysis of tracer decay.[7,8] We could fit our data obtained from the deuterium images to the biexponential form.

Blood flow measurement with an imaging coil for deuterium reflects the mean tissue blood flow parameter for the entire tissue sample more homogeneously than the spectroscopic monitoring. This technique can be much more useful when the time resolution is improved, as at present it takes about 30 sec to obtain one image including disk access delay. This imaging time resolution would be too great if we wanted to analyze first uptake perfusion phase. The acquisition time for one image in this study is less than 10 msec, but we will be able to use faster imaging sequences developed recently and the higher time resolution can be achieved when the hard-disc access delay is decreased.

REFERENCES

1. Kim SG, Ackerman JJH. Quantitative determination of tumor blood flow and perfusion via deuterium nuclear magnetic resonance spectroscopy in mice. *Cancer Res* 48: 3449–3453, 1988.
2. Corbett RJT, Laptook AR, Olivares E. Simultaneous measurement of cerebral blood flow and energy metabolites in piglets using deuterium and phosphorus nuclear magnetic resonance. *J Cereb Blood Flow Metab* 11: 55–65, 1991.
3. Detre JA, Subramanian VH, Mitchell MD, Smith DS, Kobayashi A, Zaman A, et al. Measurement of regional cerebral blood flow in cat brain using intracarotid ^2H_2O and ^2H NMR imaging. *Magn Reson Med* 14: 389–395, 1990.
4. Ackerman JJH, Ewy CS, Becker NN, Shalwitz RA. Deuterium nuclear magnetic resonance measurements of blood flow and tissue perfusion employing ^2H_2O as a freely diffusible tracer. *Proc Natl Acad Sci USA* 84: 4099–4102, 1987.
5. Ackerman JJH, Ewy CS, Kim SG, Shalwitz RA. Deuterium magnetic resonance *in vivo*: The measurement of blood flow and tissue perfusion. *Ann NY Acad Sci* 508: 89–98, 1987
6. Mitchell MD, Osbakken M. Estimation of myocardial perfusion using deuterium nuclear magnetic resonance. *Magn Reson Imaging* 9: 545–552, 1991.
7. Kim SG, Ackerman JJH. Multicompartment analysis of blood flow and tissue perfusion employing D_2O as a freely diffusible tracer: A nobel deuterium NMR technique demonstrated via application with murine RIF-1 tumors. *Magn Reson Med* 8: 410–426, 1988.
8. Kim SG, Ackerman JJH. Quantification of regional blood flow by monitoring of exogenous tracer via nuclear magnetic resonance spectroscopy. *Mag Reson Med* 14: 266–282, 1990.
9. Ewy CS, Ackerman JJH, Balaban RS. Deuterium NMR cerebral imaging *in situ*. *Magn Reson Med* 8: 35–44, 1988.
10. Haining JL, Turner MD, Pantall RM. Local cerebral blood

flow in young and old rats during hypoxia and hypercapnia. *Am J Physiol* 218: 1020–1024, 1970.

11. Nilsson L, Siesjo BK. The effect of phenobalbitone anaesthesia on blood flow and oxygen consumption in the rat brain. *Acta Anaesth Scand Supple* 57: 18–24, 1975.
12. Hayes CJ, Palmer JD. The suppression of mouse spontaneous locomotor activity by the ingestion of deuterium oxide. *Experientia* 32: 469–470, 1976.
13. Kanwar KC, Verma R. Oral D_2O administration and enzymatic changes in rat testis. *Acta Biol Med Ger* 35: 577–581, 1976.
14. Kanwar KC, Verma R. Biologic effects of orally administered deuterium oxide on rat liver. *Exp Pathol* 13: 255–261, 1977.
15. Brereton IM, Irving MG, Field J, Doddrell DM. Preliminary studies on the potential of *in vivo* deuterium NMR spectroscopy. *Biochem Biophys Res Commun* 137: 579–584, 1986.
16. Mattiello J, Evelhoch JL. Relative volume-average murine tumor blood flow measurement via deuterium nuclear magnetic resonance spectroscopy. *Magn Res Med* 18: 320–334, 1991.
17. Evelhoch JL, McDouall JBL, Mattiello J, Mattiello J, Simpson NE. Measurement of relative regional tumor blood flow in mice by deuterium NMR imaging. *Magn Res Med* 24: 42–52, 1992.
18. Branch CA, Helpern JA, Ewing JR, Welch KMA. ^{19}F NMR imaging of cerebral blood flow. *Magn Res Med* 20: 151–157, 1991.
19. Neil JJ. The validation of freely diffusible tracer methods with NMR detection for measurement of blood flow. *Magn Res Med* 19: 299–304, 1991.