Arterial Spin Labeling Blood Flow Magnetic Resonance Imaging for the Characterization of Metastatic Renal Cell Carcinoma[1]

Cedric De Bazelaire, MD, Neil M. Rofsky, MD, Guillaume Duhamel, PhD, M. Dror Michaelson, MD, PhD, Daniel George, MD, David C. Alsop, PhD

Rationale and Objective. This study sought to assess the feasibility of arterial spin labeling (ASL) blood flow (BF) magnetic resonance imaging (MRI) for the study of metastatic renal cell carcinoma (RCC) in the body, where the respiratory, cardiac, and peristaltic motions present challenges when applying ASL.

Materials and Methods. ASL was performed using a background-suppressed single-section flow-alternating inversion recovery (FAIR) preparation and a single-shot fast spin-echo imaging sequence on a 3.0-T whole body imager. Tumor BF was evaluated for 26 patients with RCC metastatic to the liver, bone, lung, or lymph nodes before VEGF receptor inhibitor therapy. Two cases with tumor size change after treatment were also scanned 1 month after therapy. For validation, kidney cortex BF in five normal volunteers was measured with the same technique and compared with literature values.

Results. ASL was successfully performed in all normal volunteers and in 20 of 26 patients. The six failures resulted from a systematic error, which can be avoided in future studies. For normal volunteers, measured kidney cortex BF was 275 ± 14 mL/min/100 g, a value consistent with the literature. ASL determined tumor BF averaged across tumor volume and subjects was 194 mL/min/100 g (intersubject SD = 100), resulting in high perfusion signal and conspicuity of lesions. Bright signal was also seen in large vessels and occasionally in bowel. In the two cases studied 1 month after therapy, ASL perfusion changes were consistent with tumor size changes.

Conclusion. With background suppression, ASL MRI is a feasible method for quantifying BF in patients with renal cell carcinoma. This technique may be useful for evaluating tumor response to antiangiogenic agents.

Key Words. MRI; arterial spin labelling; renal cell carcinoma; antiangiogenesis; blood flow.

Tumor blood flow has been suggested as a predictive parameter in the treatment of tumors with radiotherapy, where a decrease in perfusion in the early stages of the treatment correlates with a low tumor recurrence after radiotherapy (1). Blood flow monitoring may help to predict the sensitivity to chemotherapy and potential of a tumor to metastasize, because the blood flow and the vascular permeability are crucial factors in the delivery of therapeutic agents and in the migration of tumor cells (2,3). Blood flow imaging may also permit the detection of tumor recurrence in the presence of tumor necrosis, and scarring (4).

The explosion of interest in tumor angiogenesis and the therapeutic treatment of cancer with antiangiogenic agents (5–7) has emphasized the importance of blood flow measurement for tumor characterization (8). While blood flow measurement with magnetic resonance imag-

Acad Radiol 2005; 12:347–357

[1] From the Department of Radiology, Beth Israel Deaconess Medical Center and Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215 (C.DeB., N.M.R., G.D., D.C.A.); and Department of Hematology/Oncology, Massachusetts General Hospital (D.M.), and Department of Adult Oncology, Dana Farber Cancer Institute (D.G.), Boston, MA 02215. Received October 8, 2004; revision received December 14, 2004; revision accepted December 14, 2004. **Address correspondence to** D.A., Division of MRI Research/E/AN226. e-mail: dalsop@bidmc.harvard.edu

doi:10.1016/j.acra.2004.12.012

ing (MRI) or computed tomography (CT) is possible by bolus injection of a contrast agent (9–11), in practice, the separation of blood flow and permeability effects remains challenging. Nuclear medicine techniques including H_2O^{15} positron emission tomography (PET) and single-photon emission computed tomography (SPECT) with several agents can provide measures of blood flow, but they have limited spatial resolution and uptake of some agents may be altered in tumors (12,13).

Arterial spin labeling (ASL) is an alternative technique for the measurement of tumor blood flow by MRI that requires no external tracers (14–18). Labeling of arterial blood is instead achieved by changing the sign of the signal of blood in the arteries outside of the tissue being studied with spatially selective inversion pulses. After time is allowed for the labeled blood to enter the tissue, an image is acquired. The flow of the negative signal in blood into the tissue decreases the image intensity. The difference between a control image without labeling and the labeled image is used as a measure of blood flow. A relatively simple theory relates the signal change to blood flow in the tissue (14,15,17,18). The ASL tracer, water, is highly diffusible so quantification is not complicated by limited vessel permeability. ASL measurements can also readily be performed in a breath hold, unlike bolus contrast studies, where tracer kinetics typically evolves over minutes. For these reasons, ASL is an attractive candidate for tumor blood flow measurement.

ASL has mostly been used for brain blood flow imaging in research applications with a limited number of body imaging demonstrations published (19–22). Several factors contribute to this limited exploration. One is that single-shot echoplanar imaging is usually used for ASL studies to minimize motion artifact but echoplanar imaging in the body often suffers from poor image quality. Even with single-shot imaging, motion between the label and control image acquisitions can produce motion subtraction errors that dwarf the small ASL-induced signal change. Thus, the respiratory and cardiac motions inherent to body imaging present challenges when applying ASL.

It is, however, possible to substantially reduce the motion sensitivity of ASL if the background signal is attenuated by a sequence of optimally timed inversion and saturation pulses (23–25). Reduction factors of greater than 50% of the background signal can be achieved with a corresponding decrease in motion-related noise and blood flow quantification errors (26). A combination of this background suppression strategy with the improved image quality provided by single-shot fast-spin echo imaging could address most of the prior limitations of ASL in body imaging.

Here, background-suppressed ASL blood flow imaging is described in 26 patients with hypervascular complex renal cell carcinoma (RCC) with multiple metastases in chest, abdomen, pelvis, and bone before therapy with a VEGF receptor inhibitor. Because no gold standard is available for tissue blood flow assessment, kidney cortex blood flow measured with background-suppressed ASL in five normal volunteers was compared with literature values for partial validation of the accuracy. The reproducibility in blood flow quantification with ASL was estimated by using the standard deviation in blood flow found within the five normal volunteers assuming low intersubject variations in the normal health condition. To highlight the feasibility of monitoring blood flow changes under antiangiogenic treatment with ASL, results from two patients imaged again after 1 month of therapy are also presented.

MATERIALS AND METHODS

Subjects

Twenty-six patients were enrolled in the study (13 women and 13 men). Subjects were participants in a study of open-label, orally administered VEGF receptor inhibitor (PTK/ZK; Novartis Pharmaceuticals, East Hanover, NJ; and Schering AG, Berlin, Germany) in patients with metastatic RCC in lung, kidney, liver, bone, adrenal glands, and lymph nodes of the abdomen or mediastinum. Specifically, the participants were part of an expansion cohort of the Phase I/II dose-escalation study using MRI techniques to assess the biologic activity of a 1200-mg/day dosage. These studies were approved by the Institutional Review Board (IRB) of Dana-Farber Partners Cancer Care (DF/PCC), and informed consent was obtained from all subjects. Inclusion of the subjects required diagnosis of RCC and evidence of progressive disease following the RECIST criteria (27): tumor growth greater than 50% or 10 cm or apparition of new lesions. Approximately two thirds of our study population had prior exposure to systemic therapies, including agents with putative antiangiogenic properties such as interferon and thalidomide. All systemic therapies were discontinued at least 4 weeks before enrollment.

All patients were studied with ASL before receiving the therapy. Many of the patients were studied again at 1