Continuous Assessment of Perfusion by Tagging Including Volume and water Extraction (CAPTIVE): a new steady-state contrast agent technique for measuring blood flow, relative blood volume fraction, and water extraction fraction

Greg Zaharchuk*, Alexis A. Bogdanov Jr., John J. A. Marota, Masao Shimizu-Sasamata, Robert M. Weisskoff*, Kenneth K. Kwong, Bruce G. Jenkins, Ralph Weissleder, Bruce R. Rosen*

*MIT-Harvard Division of Health Sciences and Technology; MGH-NMR Center, Center for Molecular Imaging Research, Stroke and Neurovascular Regulation Laboratory, and Department of Anesthesiology,MGH, Charlestown, MA

It is becoming increasingly evident that to truly understand the functional status of an organ system, co-registered measurements of tissue blood flow and blood volume fraction are necessary. There are significant limitations to current techniques, such as bolus-tracking, especially for repeated measurements of these parameters.

We describe a new technique, CAPTIVE, that is a synthesis of arterial spin labeling (ASL) blood flow and steady-state susceptibility contrast relative blood volume measurements. Using a single injection of a novel, long half-life, intravascular contrast agent with a high tissue:blood susceptibility difference ($\Delta\chi$) to ΔR1 ratio, we measured changes in tissue transverse relaxivity arising from changes in blood volume, while preserving the perfusion contrast of traditional T1-based ASL techniques. This allows for continuous measurement of both blood flow and blood volume. Because the contrast agent can be used to remove the signal from intravascular spins, it is possible to measure the water extraction fraction. To validate CAPTIVE, we measured the CO2-reactivity of flow and volume in the rat brain.

Theory

The ASL flow equation can been modified for changes in tissue R2 or R2* and the loss in labeling at the image plane that occurs upon introduction of a contrast agent:

$$f = \frac{\lambda}{T_{1b}} \frac{S_{control} - S_{label}}{S_{label} + (2\alpha_{post} - 1)S_{control}}$$

where

$$\alpha_{post} = \alpha \exp(-\Delta R1\ \Delta t)$$

The $\Delta\chi/\Delta$R1 ratio of the contrast agent must be high enough to create significant tissue ΔR2 or ΔR2* under conditions where the increase in blood R1 leads to a small decrease in the loss of the label during the transit time (Δt) between the label and image planes, i.e., $\Delta R1 * \Delta t << 1$.

At equilibrium, the partition of the label between the blood and tissue is determined by the water extraction rate. If imaging is performed at a TE much greater than the doped blood's T2, the perfusion signal from intravascular spins can be suppressed, allowing measurement of the water extraction-flow product, EF.

Methods

We used a long-lived intravascular contrast agent, MPEG-PL-DyDTPA based on a structure, similar to its Gd-labeled analog (1). Sprague-Dawley rats (n=10, 280-380 g) were imaged at 4.7 T with 0.75% halothane. For the measurements of rCBV and CBF reactivity to CO_2, ventilated animals (n=5) were used with a dose of 125 µmol Dy/kg. Single-coil ASL imaging was performed using spin echo EPI (TR/TE: 4 s/40 ms). Labeling efficiency α was measured pre- and post-contrast agent administration. λ and brain T1 were assumed to be 0.88 and 1.5 s, respectively. Micro- and total vascular relative cerebral blood volume (rCBV) was measured using spin (4 s/80 ms) and gradient (4 s/30 ms) echo EPI, respectively.

Results and Discussion

The molar susceptibility of MPEG-PL-DyDTPA was measured to be 6.5×10^{-7}/mM Dy. ΔR1 and ΔR2 were 0.5 s^{-1} and 15 s^{-1}, respectively. At physiological dilution, the $\Delta\chi/\Delta$R1 ratio was 0.48 ppm-s, 7 times greater than Gd-DTPA. T1 and T2 for arterial blood in 3 animals at the same dose was 1.1±0.1 s and 9.6±0.3 ms, respectively. The degree of spin labeling did not change significantly post -contrast. The average (α=0.68±0.02) was used to calculate perfusion.

Figure 1 presents the key results of CAPTIVE, showing significant perfusion contrast maintained in the presence of the blood volume contrast agent. The rCBV images have 2:1 gray: white matter contrast. The % change in micro- and total vascular rCBV per mmHg $PaCO_2$ was measured to be 2.1% and 1.8% respectively. CBF reactivity was .054 (ml/g/min)/mmHg; the slope of EF was .045 (ml/g/min)/mmHg. This corresponded to a % change per mmHg $PaCO_2$ of 3.7% for CBF and 3.4% for EF. This relationship, with flow changes greater than volume changes, is consistent with other studies (2, 3).

Figure 2 shows extraction fraction vs. CBF, showing a decrease at high flow rates. PS was estimated to be 2.92±0.39 $cm^3/g/min$, and did not vary significantly with flow. For all measurements, there was no relationship between E and contrast agent dose.

Conclusions

We have described and validated a novel continuous blood flow and volume technique, dubbed CAPTIVE, which is a synthesis of steady-state susceptibility contrast imaging and arterial spin labeling. We have found that it is also capable of estimating the water extraction fraction in a straightforward manner.

References

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3. Grubb, R. L., et. al., *Stroke* **5**: 630-639 (1974).

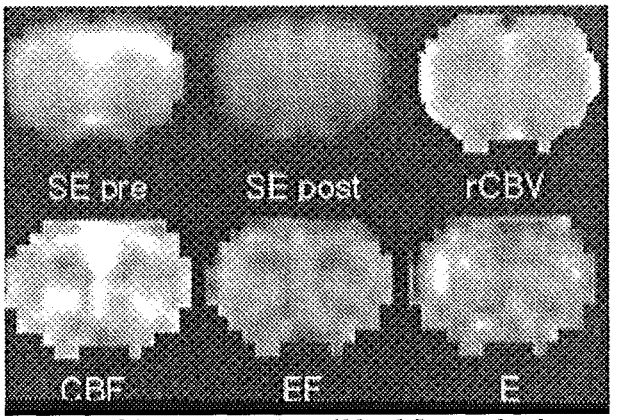

Figure 1: CAPTIVE imaging of blood flow and volume.

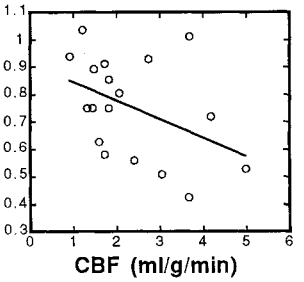

Figure 2: Extraction fraction vs. CBF