Comparison of Arterial Input Functions obtained from Unlabeled- and ^{14}C-labeled-Gadolinium-diethylenetriaminepentaacetic acid and its application in MRI Estimation of Blood-to-Brain Influx and Cerebral Microvascular Blood Space

K. Karki[1,2], T. N. Nagaraja[3], J. R. Ewing[1,2], J. D. Fenstermacher[3], and R. A. Knight[1,2]

[1]Dept. of Neurology, Henry Ford Hospital, Detroit, MI, United States, [2]Dept. of Physics, Oakland University, Rochester, MI, United States, [3]Dept. of Anesthesiology, Henry Ford Hospital, Detroit, MI, United States

Introduction

Changes in blood-to-brain transfer constant (K_i) and cerebral microvascular blood volume (v_D) measured by dynamic contrast-enhanced MRI and Patlak plots are important indicators of blood-brain barrier (BBB) pathology and angiogenesis, and have been determined for various disease models[1, 2]. The arterial input function (AIF) of contrast agent (CA) must, however, be accurately determined to calculate such parameters.[3] After a bolus injection, blood CA levels are repeatedly measured in a large cerebral blood vessel such as the sagittal sinus. Most MR sequences used for these measurements average the signal across several minutes and may not adequately capture the peak blood CA levels. If the latter is true, then K_i and, especially, v_D will be inaccurately estimated by Patlak plotting. In contrast to MRI, peak blood levels after a radiotracer injection can be readily determined by quick, repetitive arterial blood sampling. Therefore, we compared AIFs from MRI and quantitative autoradiography studies using, for the first time, identically prepared CAs viz., unlabeled- and ^{14}C-labeled- gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA and Gd-[^{14}C]DTPA, respectively). A rat model of transient focal cerebral ischemia that results in acute BBB opening[1] was employed to test the hypothesis that the AIF generated from Gd-[^{14}C]DTPA can be used to correct MRI-derived estimates of K_i and v_D.

Methods

Custom-synthesized ^{14}C-radiolabeled DTPA (Specific activity = 30.69 mCi/mmol) was purchased from New England Nuclear (MA, USA). Unlabeled and ^{14}C-labeled versions of Gd-DTPA were prepared using published methods[4]. Male Wistar rats (~300 g; n=12) were subjected to focal cerebral ischemia by suture occlusion of the right middle cerebral artery for 3 hours followed by reperfusion via suture withdrawal. T_1-weighted, Look-Locker contrast-enhanced imaging of BBB function was performed by giving Gd-DTPA as an i.v. bolus 2.5 hours after reperfusion. The AIF was monitored for 20 min via changes in sagittal sinus R_1 values (ΔR_1; $R_1=1/T_1$)[1]. After the MRI study, the rats were injected with a bolus of Gd-[^{14}C]DTPA. The tracer was allowed to circulate for 20 min and timed arterial blood samples were taken to establish the AIF. Data from these curves were normalized across experiments by expressing each value as a percentage of the last (20th min) value. The MRI-AIF for each experiment was reconstructed with the missing early time data points calculated based on the values from the Gd-[^{14}C]DTPA-AIF. Patlak plots were constructed using the T_1 Look-Locker data, and K_i and v_D were estimated for both the original and reconstructed MRI-AIFs. Data were expressed as mean ± standard deviations. Differences were examined by paired t-tests and significance was inferred at $P \leq 0.05$.

Results

The MRI-AIF was constructed using ΔR_1 values obtained approximately every 2.5 min after bolus injection (e.g., Fig. 1A). The Gd-[^{14}C]DTPA-AIF from the same rat is shown in Fig. 1B. This AIF was much sharper, and peak blood levels were effectively captured. The reconstructed MRI-AIF is shown in Fig. 1C and was larger than the original one as measured by their arterial integrals (AI; Table 1). For the regions with a leaky BBB, the reconstructed MRI-AIF produced significantly lower values of K_i and v_D than did the original (Table 1).

Conclusions

Including the missing blood data in the MRI-AIF resulted in lower, more accurate K_i and v_D estimates. However, the effect on K_i was relatively smaller than that on v_D, owing to different characteristic times of response for contrast leakage to the tissue, which behaves like a low-pass filter, and the vasculature, which has much faster response times to the input. The missing part of the MRI-AIF was remarkably consistent across experiments, which suggests that a universal correction factor might be included in the MRI-AIFs from contrast injection studies to derive better estimates of capillary permeability, microvascular blood volume, and changes in these physiological functions.

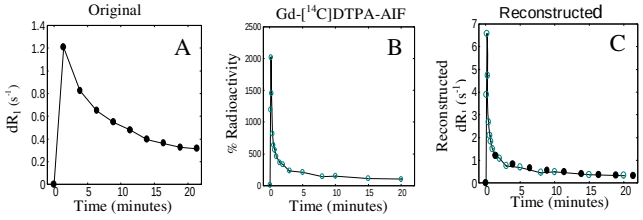

Fig.1. An example of the three different AIFs generated from one experiment. Note the differences in peak plasma CA levels and the shape of the input function given by A and C. The filled circles in C represent the data shown in A.

Table 1. Plasma AI values and K_i and v_D values from leaky BBB regions with the original and reconstructed (Recon.) AIFs. Employing the original AIF resulted in significant overestimation of both K_i and v_D.

Parameter	Original	Recon.	P
AI	650.6±143.7	796.9±200.0	0.005
K_i (10^{-3} min^{-1})	2.808±0.661	2.488±0.551	0.0005
v_D (10^{-2})	4.612±1.083	3.502±1.055	0.0009

References

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