Assessment of Vascular Permeability in Calf with Dynamic Contrast MRI

C. S. Zuo[1], R. I. Dobbins[2], D. J. Nunez[2], R. Villafuerte[1], M. Butman[1], M. E. Henry[1], B. S. Oraban[2], A. P. Brown[2], J. Brown[2], and P. F. Renshaw[1]

[1]McLean Hospital, Harvard Medical School, Belmont, MA, United States, [2]GlaxoSmithKline

Introduction

Dynamic T1-weighted MRI in conjunction with Gd-DTPA is a promising method for investigating breakdown of the blood-brain barrier (1,2). In the lower extremities, most of dynamic contrast MRI studies have been devoted to detection of abnormal blood flow in major or peripheral vessels (3). The purpose of this study is to investigate the feasibility of dynamic contrast MRI for estimation of vessel permeability in calf muscle of healthy control.

Materials & Methods

Subjects: The study was conducted in 6 healthy, young male subjects (age: 28±5, body weight 160±12 lbs) under a protocol approved by the IRBs of relevant institutions. Gadopentetate dimeglumine (GdDTPA, Berlex Laboratories, Wayne, NJ, USA) was injected at the recommended clinical dosage of 0.1 mmol/kg intravenously using a power injector at a rate of 3cc/sec followed by 20cc of saline flush at 0.3cc/sec.

MRI: The dynamic contrast MRI was conducted on a 3T MR scanner (Trio, Siemens AG, Germany) using a CP volume coil for transmission and reception. The MR exam consisted of baseline, dynamic, and post contrast T1 measurement as follows: (i) Baseline T1 values of blood and muscles were determined by averaged of 4 measurements of a multi-TI turbo FLASH sequence (TR/TE/FA = 9000/1.2/8˚ with time intervals 2.4ms between acquisition of each line in k-space, acquisition matrix 64x128, FOV 260, slice thickness 8mm) at TI values of 100,200,350, 500,700,900,1500ms, and ∞. (ii) Dynamic T1 measurements synchronized with the injection were performed with a single-shot turbo FLASH sequence near the null point of calf tissue (~450ms) (TR/TE/FA = 9300/1.2/8˚) for 4 minutes. (iii) 4 minutes post contrast injection, T1 was measured by the multi-TI turbo FLASH sequence at the same TR/TE/TI values as in (i). The multi-TI T1 measurement was repeated at intervals of 5 minutes to monitor the T1 values until 20 minutes post GdDTPA injection.

Data analysis: T1s of blood and tissue at baseline and post contrast were calculated from least square fits of the multi-TI inversion recovery images. For the dynamic T1 measurement, regions of interest (ROIs) were placed within the main vessels for estimating the blood T1 and regions near the peroneal vein and artery and posterior tibial vessels in the soleus and tibials posterior muscles across the time series of the images to estimate leakage of GdDTPA from the vessels. T1 changes of the blood and the tissue were calculated from the corresponding signal changes based on the signal vs T1 relationship (2). Area under the curve of the tissue R1 (=1/T1) versus time between the arrivals of the contrast and the R1 reaching its maximum was used to estimate the relative volume of the contrast reached tissue compartment. Specific relaxivity of the GdDTPA was measured to be 4.0Hz/mM at ~25C at 3T by measurement of T1s of a series of saline phantoms at different GdDTPA concentrations.

Results

At baseline, blood has a T1 of ~1.4secs, and muscle T1 ~1sec, consistent with literature reported values (4). Four minutes after the contrast injection, blood and muscle T1s were still shortened to ~0.4sec and 0.72 sec respectively, implicating that there was still a significant amount of GdDTPA in blood. Dynamic T1 measurement indicated that MR signal intensity of blood experienced a rapid increase and plateau ~40secs after the contrast injection while the signal of the tissue monotonically increased at a much slower pace (Figure 1). The arrival time to the local blood vessels is consistent with values reported previously (3). The blood signal then remained at its plateau and muscle signal increased monotonically. The much slower increase of the muscle signal intensity suggests that it was due to leakage of GdDTPA from blood vessels into tissue.

The blood and tissue signals were converted into changes in the T1 relaxivities and the initial slope of the tissue reflexivity change curve (Figure 2) indicate the permeability-surface-area-product values range from 0.019 to 0.049 min^{-1} (mean 0.035+/-0.012 min-1, n=6) in the regions of the muscles (2,5). A "perfused" volume map can be generated based on the integration of R1 change versus time (Figure 3), which indicates a relative variation among gastrocnemius, soleus, and tibialis muscles.

Discussion

Increased microvascular permeability induces leakage of proteins or plasma from the intravascular to the extravascular space. This leakage may occur as a side effect of medication and is a physiologic event of great clinical significance. Conversely, a medication that reduces microvascular permeability or increases protein permeability could be of value to maintain normovolemia and to reduce the need for plasma substitutes. On the other hand, an agent such as nifedipine (6,7) that may increase vascular permeability would require closely monitoring on possible increase of vascular leakage during use. Evens blue and other dyes have been the standard method for measurement of vascular permeability (8,9). However, their invasiveness and possible side effect in patients have limited their application in clinical diagnosis and treatment monitoring.

Most of the MR vascular permeability values have been reported to tumor in brain and regions with vascular barrier under pathological conditions (5,10,11). To our knowledge, few measurements have reported in calf muscle. Our results are well within the ranges of reported values in the literature from regions other than calf and suggest that dynamic contrast MRI can be used to quantify vessel permeability in the calf.

Acknowledgement

This study was supported in part by a grant from GSK (MEH) and by a grant from NARSAD (YI 2004) and grants from NIH (DA15116, 14178, and 09448).

Reference:

1. Li K, Zhu X, Waterton J, Jackson A. JMRI 2000;12(2):347-357.
2. Tofts P, Kermode A. Magn Reson Med 1991;17(2):357-367.
3. Prince M, Chabra S, Watts R, et al. Radiology 2002;224(1):55-61.
4. Stanisz G, Odrobina E, Pun J, et al. MRM 2005;54(3):507-512.
5. Li K, Zhu X, Checkley D, et al. Br J Radiol 2003;76(901):39-50.
6. Lacolley P, Poitevin P, Koen R, Levy B. J Hypertens 1998;16(3):349-355.
7. Taherzadeh M, Das A, et al. Am J Physiol 1998;275(4 Pt 2):H1388-1394.
8. Saria A, Lundberg J. J Neurosci Methods 1983;8(1):41-49.
9. Warnick R, Fike J, Chan P, et al. J Neurosci Methods 1995;58(1-2):167-171.
10. Berkowitz B, Roberts et al. Invest Ophthalmol Vis Sci 2004;45(7):2391-2398.
11. Provenzale J, Wang G, et al . AJR Am J Roentgenol 2002;178(3):711-716.

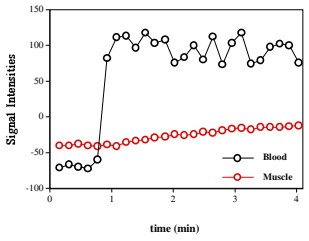


Figure 1 Representative plots of MR signals of blood (black) and muscles (red) vs time shortly before and minutes after contrast injection.

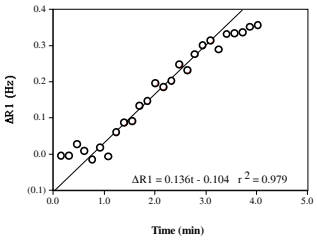
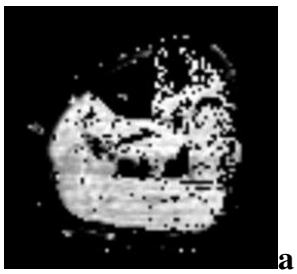


Figure 2 Change in T1 relaxivity (ΔR1) of muscle near the peroneal vessels shortly before and minutes after contrast injection.


a

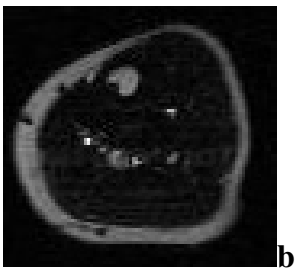

b

Figure 3 A representative map (**a**) of perfused regions in the calf cross section (**b**). The map was generated by summing the area under the tissue ΔR1 between the time the contrast arrived and the time ΔR1 reached its maximum/plateau.