High Resolution *Q*-maps of Mouse Brain Microvasculature

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Introduction Histologic studies of tissue samples commonly use the density of capillaries and other small vessels to quantify microvasculature. In particular, the intra-tumoral microvessel density is an established measure of angiogenic activity in solid tumors and is strongly correlated with tumor prognosis [1]. Microvessel density is also of interest in the study of ischemia and aging [2]. The measurement of the relative blood volume with contrast-enhanced MRI techniques has been used to quantify microvasculature in vivo [3,4]. However, because blood volume depends on the average size of microvessels, as well as their density, blood volume alone may not be a reliable indicator of microvessel density [5]. Microvessel size and density are both variable within normal tissue structures and, even more so, within tumors. For this reason, an MRI technique that yields estimates for vessel size has also been utilized [6]. Given the vessel size and blood volume, the microvessel density may be inferred. A closely related alternative method is to measure an index, referred to as *Q*, that is sensitive to the microvessel density but not the vessel size [7]. In addition, the quantity *Q* has the advantage of being insensitive to the contrast agent concentration, as long as the dose exceeds a threshold [7]. On the other hand, the vessel size index, as it is conventionally measured, requires that the intravascular contrast agent concentration be known [6]. Here, we present high resolution *Q*-maps of normal mouse brain. Our results provide normative cerebral *Q* values and indicate significant regional variations. Good agreement is demonstrated between microvessel density estimates derived from the *Q*-maps and published values obtained from histological sections.

Theory Consider imaging an animal before and after the injection of a superparamagnetic intravascular contrast agent. Let S_{pre} and S_{post} be the pre-contrast and post-contrast signal intensities for single spin echo (SSE) images, and let S_{pre}^* and S_{post}^* be the pre-contrast and post-contrast signal intensities for gradient echo (GE) images. Then define the transverse relaxation rate shifts: $\Delta R_2 = \ln(S_{pre} / S_{post})/\text{TE}$, $\Delta R_2 = \ln(S_{pre}^* / S_{post}^*)/\text{TE}$, where TE is the echo time. The quantity Q is then given by $Q \equiv \Delta R_2 / (\Delta R_2^*)^{2/3}$. For a random cylinder model of the vascular network, one can demonstrate that $Q=1.678k(DN)^{1/3}$, as long as the contrast agent concentration is sufficiently high, the blood volume fraction f is sufficiently small, and the echo time is neither too short nor too long [7]. Here, D is the self-diffusion coefficient for water, and N is the microvessel density. If the distribution of vessel radii is narrow, then the dimensionless parameter $k \approx 1 - 0.44(\delta^2 R / R_0^2)$, where R_0 and $\delta^2 R$ are the average and variance for the distribution. Q is independent of the contrast agent concentration and can be regarded as an intrinsic tissue property [7]. Note that while Q does depend on the relative width of the vessel distribution, it is independent of the absolute scale. Aside from the dimensionless factor, which relates to the details of the vessel distribution, Q is sensitive just to the microvessel density and the diffusion coefficient. Since the diffusion coefficient can be independently measured with MRI, an estimate for Q can be used to obtain in vivo estimates for the microvessel density N. In normal brain, the average microvessel radius is about 4.0 ± 0.7 μm [5], therefore $k \approx 0.99$, as long as the presence of macrovessels can be neglected. The average water diffusion coefficient in the cortical and subcortical regions of rat brain is about 0.664 ± 0.008 μm^2/ms and shows remarkably little regional variation [8]. Combining these results then yields the $N \approx Q^3 \times 329$ s/mm^2.

Methods The experiments were performed on a Bruker 9.4 Tesla microimaging system (Bruker NMR, Inc., Billerica, MA). Multi-slice axial brain images were obtained for six 4-month-old wild-type adult mice (25-30g) both before and after the injection of a 30 mg Fe/kg dose of MION. The post-contrast image acquisition was delayed by 5 minutes to ensure a steady state distribution of MION in the vascular network. Two pulse sequences [4] were used: i) 3D GE with TR/TE = 40 ms/5.5 ms, flip angle = 5º, acquisition matrix = 192 × 192 × 16, and NEX = 8; and ii) 2D multislice SSE with TR/TE = 2000ms/30 ms, flip angle = 90º, acquisition matrix = 192 × 192, and NEX = 6. For all the sequences, the slice thickness was 600 μm and the in-plane resolution was 100 μm. The dosage and echo times used here are in a validated range (7) for applying *Q*-map theory to our experimental results.

Results Axial ΔR_2, ΔR_2^*, and *Q*-map images obtained from one animal are shown in Fig. 1. By converting our *Q* values into an estimated microvessel density *N*, average *N* values for eight regions of interest and for the entire brain region were determined (Fig. 2). The average *N* value of the entire brain is 282 ± 43/mm^2, which is in reasonable accord with the histologically determined values for rat brain of 277 ± 118/mm^2 given by Weiss et al. [9] and 370 ± 94/mm^2 given by Pathek et al. [5]. A significant regional variation in the *N* values can be seen. In particular, the average difference between the microvessel densities in the cerebral cortex and the hippocampus is 206 ± 57/mm^2. The regional microvessel densities in cerebral cortex, hippocampus, thalamus, superior colliculus, and inferior colliculus are also comparable to those found by Klein et al. using histological methods [10].

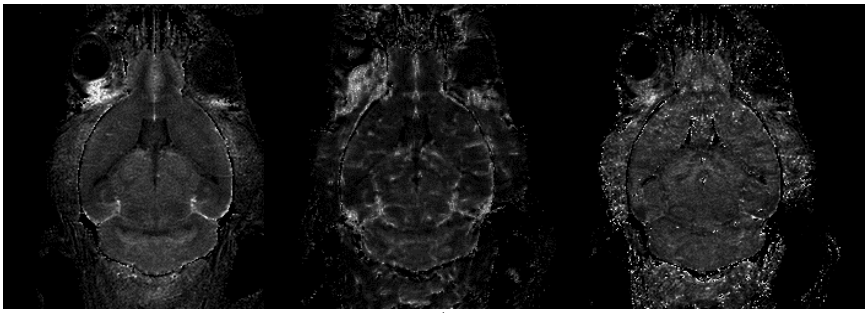

Fig. 1 Axial calculated ΔR_2 (left), ΔR_2^* (middle), and *Q*-map (right) images

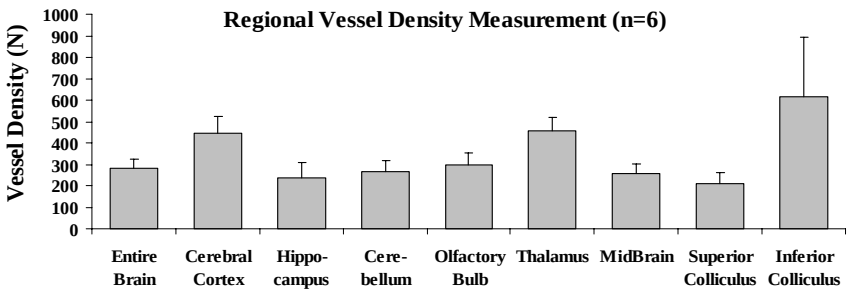

Fig. 2 Average microvessel density values for different ROIs

Conclusion In conclusion, the acquisition of *Q*-maps with MRI is potentially a practical in vivo method of quantifying microvessel density. It may be useful in the assessment of tumors and disease processes associated with angiogenesis and other vascular abnormalities. The development of rapid imaging techniques that allow *Q* to be measured from the first pass of a contrast agent bolus would greatly enhance the feasibility of the method for clinical studies.

References **1**. Hasan J et al. Br J Cancer 64:1566, 2002. **2**. del Zoppo GJ et al. J Cereb Blood Flow Metab 23: 879, 1995. **3**. Le Duc G et al. MRM 42:754, 1999. **4**.Wu EX et al. MRM 49:765, 2003. **5**. Pathak AP et al., MRM 46:735, 2001. **6**. Troprès I et al., MRM 45:397, 2001. **7**. Jensen JH & Chandra R. MRM 44:224, 2000. **8**. Hoehn-Berlage M et al., NMR Biomed12:45, 1999. **9**. Weiss HR, et al. Circ Res 51:494,1982. **10**. Klein B et al. Am J Physiol 251:H1333, 1986.