Contribution of Perfusion in Diffusion Weighted MRI of Orthotopic and Subcutaneous Hepatocellular Carcinoma in Rat

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Introduction
As a quantitative parameter calculated from diffusion weighted (DW) ¹H MRI, apparent diffusion coefficient (ADC) of water may reflect not only diffusion that represents mostly the Brownian motion of the water molecules, but also perfusion in microvessels. It can explain a very wide range of ADC values reported for the liver and hepatocellular carcinoma (HCC) in both animals (1, 2) and humans (3, 4). Previous studies show that for low b-values (< 100 s/mm²) perfusion dominates diffusion by a factor of 10. However, by using high b-values (> 500 s/mm²), the influence of perfusion is largely attenuated (5). We compared the perfusion (b-values = 0, 10, 20, 30, and 100 s/mm²) and diffusion (b-values = 220, 350, 600, 1000, and 1600 s/mm²) components in the rat liver, and intrahepatic and subcutaneous HCCs. The objective of the study was to evaluate the possible contribution of capillary tissue perfusion and water molecular diffusion in DW ¹H MRI of HCCs located intrahepatically and subcutaneously.

Methods
DW ¹H MRI was performed on Sprague-Dawley rats. Each animal was imaged 21 days after injection of 1 × 10⁶ N1S1 cells into the left liver lobe or on 28 days after injection of 10 × 10⁶ cells under the skin on the thigh. MRI images were acquired with a Varian 9.4 T, 31-cm horizontal bore system. The water ADC of the HCCs and normal liver tissue was measured with a 63-mm birdcage coil. A multi-slice DW ¹H imaging sequence with the following imaging parameters was used: 1,100 ms repetition time, 21 ms echo time, 256 × 128 data points over a 80 × 80 field of view, 0.5 mm slice thickness, 1.5 mm slice gap, and b = 0, 10, 20, 30, 100, 220, 350, 600, 1000, and 1600 s/mm². Respiratory gating was used to minimize the effects of motion on water ADC measurement. Total data collection time for a set of DW ¹H MRI at 10 b-values was ~ 23 min. DW MRI signal intensity (SI) versus b value data were fit to the following biexponential equation for normal liver and intrahepatic HCC: SI = A₀₁ × e⁻ᵦ₁ × ADC₁ + (1 – A₀₁) × e⁻ᵦ₀ × ADC₀, where A₀ is SI for a b = 0 s/mm², ADC₀ and ADC₁ are the fast and slow ADC components which are related to tissue perfusion and random molecular diffusion of water, respectively, and A₀₁ is the relative contribution of ADC₁ which is related to the relative vascular volume or the fraction of fast moving ADC. A monoexponential equation was used for subcutaneous HCC. PSI-PLOT software was used to analyze ADC₀ and ADC₁ components.

Results
Transaxial sections of DW ¹H MRI of the rat liver, intrahepatic, and subcutaneous HCC collected using ten b-values are shown in Fig. 1. In intrahepatic and subcutaneous HCCs, SI b= 0 s/mm² was almost 2 and 1.5 times higher respectively, compared to normal liver (Fig. 2). In normal liver and intrahepatic HCC, the curves that describe the DW ¹H SI changes with different b-values was biexponential. A₀ in control liver was 0.31, while the values of ADC₀ and ADC₁ were 20.2 and 0.70 s/mm², respectively (Table 1). In intrahepatic HCC, A₀ was 0.38, while the value of ADC₀ was lower (9.35 s/mm², P = 0.05) and ADC₁ was similar (0.70 s/mm²) compared to the healthy liver. In subcutaneous HCC, the curve that describes the DW ¹H SI changes with different b-values was monoexponential, reflecting very poor development of the circulatory system (Fig. 1). In this HCC model, ADC₁ (0.65 s/mm²) did not differ compared to intrahepatic HCC and liver (Table 1).

Discussion
Water ADC measurements in HCC, metastases, and hepatic angiomata are higher than those of hepatic parenchyma (4). These measurements, however, may include a contributory perfusion component, particularly in tissues with a rich vasculature such as intrahepatic HCC. The data presented here shows that ADC₀ and ADC₁, which contributes 38% to the total signal in intrahepatic HCC, is significantly lower compared to the normal liver value. This decrease may be because of restricted perfusion in abnormal tumor microvessels. Respiratory motion may also contribute to ADC₁, because the motion artifact was clearly visible in liver bearing HCC. However, the motion did not affect ADC₀ which was similar to that of subcutaneous HCC that is insensitive to abdominal motion. Thus, simultaneous monitoring of water ADC changes in intrahepatic and subcutaneous HCCs may be useful, but the possibility of location-based physiological and metabolic differences must be recognized. Vascular architecture and thus its response to therapy not only vary among tumor types, but may differ between transplanted and spontaneous tumors (6). These differences may lead to different altering in ADC to chemo-, radio-, or immunotherapy.

Conclusion
A biexponential model for analysis of non-invasive DW ¹H MRI provides important information about neoplastic transformation in capillary liver tissue perfusion and water molecular diffusion. Recognition of both perfusion and diffusion components of water ADC may be important for monitoring tumor growth and response to therapy of orthotopic and metastatic HCC.


Fig. 1. Representative transaxial slices of DW ¹H MRI of the rat liver, intrahepatic (IH) and subcutaneous (SC) HCC with different b values. HCCs are marked by arrow and liver is marked by dotted line. b-values are in s/mm². Ref. – reference (0.3 mM NaCl).

Fig. 2. Perfusion and diffusion component of ADC in the rat liver, intrahepatic and subcutaneous HCCs (mean ± SEM, n = 8). The signal intensity in liver with b = 0 s/mm² is normalized to 100. Shading indicates the perfusion component area.

Table 1. Fast and slow components of water ADC in the rat liver, intrahepatic (IH) and subcutaneous (SC) HCC.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Liver</th>
<th>IH-HCC</th>
<th>SC-HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>A₀</td>
<td>99 ± 7</td>
<td>193 ± 15°</td>
<td>163 ± 9°</td>
</tr>
<tr>
<td>A₀₁</td>
<td>0.31 ± 0.05</td>
<td>0.38 ± 0.05</td>
<td>0.05 ± 0.05</td>
</tr>
<tr>
<td>ADC₀</td>
<td>20.2 ± 5.3</td>
<td>9.35 ± 1.62°</td>
<td>-</td>
</tr>
<tr>
<td>ADC₀₁</td>
<td>0.70 ± 0.08</td>
<td>0.70 ± 0.09</td>
<td>0.65 ± 0.02</td>
</tr>
</tbody>
</table>

Note. ADC values are in 10⁻³ mm²/s. *P ≤ 0.5 (vs. Liver)