MRI as a novel tool for monitoring liver hemodynamics

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Background/ Aims:
Many liver diseases, as cirrhosis and cancer, involve hemodynamic changes. Currently, there are limited tools for monitoring these changes in the liver and they are invasive or ex-vivo. In liver regeneration, hepatocyte proliferation precedes the angiogenic process. Consequently, liver hemodynamics are immensely affected till regeneration concludes. In cirrhosis, reduced liver sinusoidal functionality results in altered hemodynamics. Those are usually observed by MRI only in late stages and by injection of Gd. Previously[1], we have demonstrated that changes in oxygen saturation, blood volume and blood flow can be detected by MRI using BOLD contrast. The aim of this study is to implement this method for monitoring hemodynamic changes in the liver, non-invasively, in order to combine anatomical and functional information in the same procedure and refine diagnosis. In order to evaluate the competence and usefulness of this method we induced different pathological circumstances involving hemodynamic changes in rats.

Methods:
MRI:
MRI experiments were preformed on a 4.7 T Bruker Biospec spectrometer using a bird cage coil. Changes in hepatic hemodynamics were evaluated from GE images acquired during breathing of air, air-CO_2 (95% air and 5% CO_2), and carbogen (95% oxygen and 5% CO_2) as described[1]. Four images were acquired at each gas mixture (slice thickness = 1.5 mm; TR/TE= 100/10 ms; FOV = 5.8 cm; 256 × 128; 4 averages). Other experimental details were as reported[1]. The change induced by carbogen (VF) signifies vascular density and tissue perfusion. The change generated by CO_2 (VD) corresponds to blood flow and volume. Data is presented in color maps overlaid on the original baseline image for |VD| and |VF| >0.005[1].
Animal models:
Portal ligation: Rats underwent ligation of the portal vein (n=3). Immediately after, they were scanned as mentioned above. **70% partial hepatectomy (PHx)** was performed on adult male Sprague-Dawley rats[2]. Rats were scanned daily before and on days 0-10 after PHx (n=5). **Liver fibrosis** was induced by IP administration of Thioacetamide (TAA) 0.2mg/g body weight twice weekly for 8 weeks. Rats were scanned weekly during the 8 weeks of TAA administration (n=4).

Results:
In healthy rats (n=15), mean VF values of the liver (0.04±0.02) are 20 times greater than those of the muscle tissue (0.002±0.02), suggesting a higher vascular density and blood content in the liver (Fig 1a,d). This is in accordance to the literature that normally 15% of the total blood volume is in the liver. Surprisingly, mean VD values of the liver are negative (-0.03±0.02) opposed to the values of muscle tissue (0.002±0.01), (Fig 1b,e). We speculated that CO_2 enrichment causes vasoconstriction to the hepatic artery, hence the liver deoxyhemoglobin level rises. In order to prove this we ligated the portal vein and observed positive values of VD (0.002± 0.01) similar to the muscle (Fig 1e). As a result of portal ligation, VF values decreased dramatically (0.005±0.009) due to the fact that blood content and blood nourishment of the liver diminished (Fig 1d).

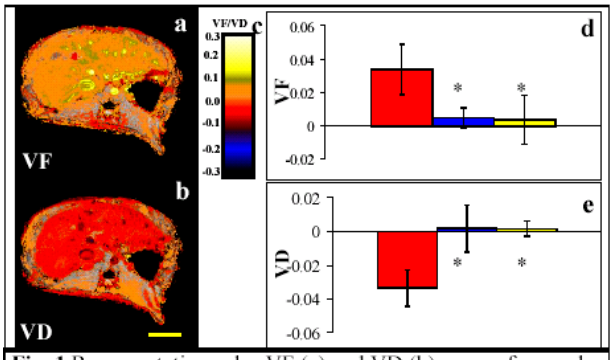

Fig. 1 Representative color VF (a) and VD (b) maps of normal rat livers. Color scale (c). Comparison between VF (d) and VD (e) values in the normal liver (■), in the liver after portal ligation (■) and in the normal muscle (■). Bar 1cm. * p<0.01 compared to normal liver.

In liver regeneration, hepatocyte proliferation precedes the angiogenic process. Consequently, liver hemodynamic is immensely affected till regeneration concludes. Indeed, after PHx, VF values decline (0.009±0.007) as perfusion and blood content decrease. As expected, when regeneration proceeds they are gradually restored. VD values ascend and become positive (0.01±0.001) signifying a change in the source of nourishment. Since there is a growing need of energy in the liver the hepatic artery becomes the main source of blood enriching the liver with oxygenated blood. VD values too are gradually restored as regeneration proceeds.
During the fibrotic process, scar tissue replaces liver tissue, therefore there is shunting and reduced perfusion. This process started as immense inflammation illustrated by the extreme VD and VF values in the first week (-0.1 ±0.03 and 0.12 ±0.05, respectively). Following that, VD values gradually turned positive (0.003±0.02) and VF values decreased (0.0006±0.007). These changes could indicate structural and functional alterations of sinusoids and portal pressure affecting hepatic hemodynamics.

Discussion:
We offer here a new and non-invasive method for monitoring liver hemodynamics without the necessity of an external contrast agent. We proved that we can follow induced hemodynamic changes. This method enabled us to follow pathological changes such as liver fibrosis at its first stages and regeneration. In future this method could be essential for monitoring liver disease and therapies.

References
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