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Magnetic Resonance Imaging of the Liver: a Move Towards Function and Quantification

Ressonância Magnética do Fígado: Avanços na Função e Quantificação

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From an invisible organ to one of the most explored non-invasively, the liver is, today, one of the cornerstones for current cross-sectional imaging techniques and minimally invasive procedures. After the achievements of US, CT and more recently MRI, in providing highly accurate morphological and structural information about the organ, a significant scientific development has gain momentum for the last decades, coupling morphology to liver function and contributing far most to what we know today as precision medicine. In fact, dedicated tailor-made investigations are now possible in order to detect and most of all quantify physio pathological processes with unprecedented certitude. Contrast enhanced imaging, diffusion weighted imaging, spectral computed tomography and fat and iron assessment techniques are commonly performed clinically. Diffusion kurtosis imaging, magnetic resonance spectroscopy, T1 relaxometry and radiomics have been more reserved to clinical research. Each of them has its own value and place on the diagnostic armamentarium and may provide unique qualitative and quantitative information regarding the pathophysiology of diseases, contributing at a large scale to model therapeutic decisions and patient follow-up. Therefore, state-of-the-art liver imaging acts today as a non-invasive surrogate biomarker of many focal and diffuse liver diseases. This opinion article is a summary of a larger review paper recently published[1] and we will discuss 3 major pathways to deliver these goals, specifically exploring molecular micro movement, liver receptor activity and quantification. They are, in our opinion, important pathways in order to deliver MR based precision medicine.

1. The case for diffusion-weighted imaging (DWI)

DWI is a technique in which the contrast is based on differences in the mobility of water molecules within a tissue after the application of sensitizing magnetic gradients. Water can easily diffuse (move freely) in tissues with a large extracellular compartment. However, when cellularity within tissues is increased (eg. high grade tumors or acutely infarcted tissues), the diffusion becomes impeded, hence the term "restricted diffusion". The movement of the water molecules within the probed tissue can be calculated and quantitated using the so called apparent diffusion coefficient (ADC) value. The higher its value the greater the water molecules displacement within a certain tissue space, also returning high signal intensity on the corresponding ADC map. As this technique is widespread on almost every recent MR platform and does not require administration of contrast agents, it is gaining increasing acceptance and is now an integral part of the MR examination of the upper abdomen.

The most established use of DWI in the liver is for the detection of focal liver lesions, particularly metastases. Current evidence shows that DWI can improve the diagnostic accuracy for the detection of hepatic metastases, and its diagnostic value increases when combined with the use of hepatobiliary-selective contrast agents for the detection of sub-centimeter range focal liver lesions.

Assessment of treatment response is another potential use of DWI. The ADC values of hepatic primary and secondary neoplasms have been shown to increase following successful treatment (e.g. chemotherapy, radiotherapy or chemoembolization), thus bringing the potential for quantitative ADC to be used as a treatment-response biomarker. High pretreatment ADC values have also been shown to predict therapy response, according to small proof-of-concept series.

Conventional DWI is based on the simplified premise of the gaussian (or normative) distribution of water diffusion in biologic systems. In reality, the complex intracellular and extracellular in vivo environment causes the diffusion of water molecules to deviate considerably from this pattern. An alteration of a normative pattern of distribution in probability theory is defined as kurtosis. Diffusion kurtosis (DKI), first proposed by Jensen et al in 2005, is an attempt to account for this variation, thus providing a more accurate model of diffusion and capturing the nongaussian diffusion behaviour as a reflective marker for tissue heterogeneity.

Recent studies suggest that DKI has additional value over conventional DWI, particularly in hepatocellular carcinoma (HCC) regarding its characterisation, assessment of treatment response and prediction of microvascular invasion. As a conclusion we may state that conventional DWI or DKI are key players for liver MRI acting as a biomarker for disease detection, characterisation and treatment evaluation.

2. The case for MR contrast agents

Extracellular fluid agents are the most widely used and best-documented contrast agents in CE imaging of the liver and in longstanding, routine clinical use. Liver imaging with extracellular fluid agents mainly relies on differential blood flow between the liver and the focal lesion/s contributing to detection and characterization. The temporal signal intensity changes that occur when using contrast enhancement may be used to provide a more in-depth perfusion analysis with a semi-quantitative approach (evaluation of time-to-peak, maximal peak intensity or washout over time relying on the evaluation of time-intensity curves). A more detailed approach, strictly quantitative, can be obtained when images are sequentially obtained over time with sufficient temporal resolution (normally in the order of 1-2 seconds) allowing the use of pharmacokinetic mathematical models). The data obtained allow a real quantification of physiological parameters indicating the functional status of the vascular system within tumours and adjacent tissues. Typically these parameters include calculation of blood flow, blood volume, mean transit time and permeability surface. This type of information although conceptually very appealing, especially for treatment response monitoring in oncologic applications, still suffers from variability among scanners and thus reproducibility issues. This is until now the main reason why this technique has not been adopted in clinical trials as a biomarker for tumor response. Hepatobiliary-specific agents have been developed during the past 3 decades, and the ones currently available for clinical use are gadobenate dimeglumine (Gd-BOPTA) and gadoxetic acid (Gd-EOB-DTPA).

These contrast agents have different pharmacokinetic behavior: they are initially distributed in the extracellular fluid compartment, similarly to extracellular fluid agents, but are subsequently taken up by organic anion transporters residing in the normal functioning hepatocytes and furthermore, again by active transport, are excreted into the bile 20 to 60 minutes after injection (depending on the agent). Hence, they provide the dual benefit of dynamic imaging capability as well as delayed hepatobiliary phase imaging.

The main clinical applications of hepatobiliary-specific contrast agents are: 1) detection of hepatic metastases 2) differentiation of nonhepatocellular from hepatocellular lesions; 3) diagnosis of focal nodular hyperplasia with a higher degree of confidence and discrimination from hepatic adenoma; 4) to provide contrast-enhanced MR cholangiography for anatomic and functional assessment of the biliary tree.

Another application is the assessment of liver function by quantifying the degree of hepatic signal intensity enhancement in the hepatobiliary phase and the presence of contrast media in the bile ducts. This has potential applications for the noninvasive prediction of residual liver function for patients proposed to major partial hepatectomy or to diagnose early liver failure after an orthotopic liver transplant graft.

3. The case for quantification

One of the major public health problems that we face today is the growing prevalence of liver steatosis and metabolic syndrome, that may act as pro-inflammatory factors promoting the development of steatohepatitis, fibrosis and finally HCC. Once we are able to to interfere with the normal course of fatty liver infiltration and fibrosis, the role of accurate non invasive quantification for diagnosis and follow-up appears promising. On MR proton density fat fraction (PDFF) calculation is a recent chemical shift–based technique that can be completed in breath hold and allows for the calculation of fat fraction in any segment of the liver. Using multi-peak fat models and low flip angles, the advantage of this technique is that it provides correction for multiple confounding factors, such as T1 bias, T2* decay, etc. It is a very simple technique, quick to perform that correlates closely with the grade of steatosis at histology. PDFF has been applied at a a larger scale in the general population and is replacing MR spectroscopy in clinical practice and clinical trials, with standardization to enable equivalent measurements across commonly used hospital MRI scanner systems. Also, the role of MR for quantification of iron deposition is quite well established and is repeatable and reproducible among techniques and imaging platforms. Today, online tools do exist that can provide direct, accurate MR based iron quantification such as the MR Quantif tool developed by academic researchers. Quantitative susceptibility mapping is a recent iron quantification technique that relies on the estimation of the impact of a susceptibility source (such as ferritin or hemosiderin) on the local magnetic field. Although being a promising method and potentially the most direct and sensitive technique for the detection of iron deposition, it is not standardized and not offered by the main MR imaging manufacturers, hence why it is still limited to research purposes.

The main goal in the near future will be to include, routinely, MR derived data of simultaneous quantification of iron and fat, irrespective of the clinical indication, offering this clinical information as an integral part of the MR study. The conditions to fulfil are easiness of performance, rapidity of acquisition and fully automatic delivery of results. if so, this important diagnostic information will became an integral component of liver MR studies or can even be used on a more widespread population based screening for NAFLD, NASH, etc.

1. Cruz A, Ferreira A, Papanikolaou N, Banerjee R, Caseiro-Alves F. New boundaries of liver imaging: from morphology to function. European Journal of Internal Medicine. 2020;79:12-22.