

Liver function and failure

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In this presentation, we will review the normal anatomy and function of the liver. We will then review the epidemiology of chronic viral hepatitis and the performance of current MRI technology applied for the evaluation of disease severity of chronic viral hepatitis, and we will finish by giving an overview on the challenges/limitations of MRI methods and what needs to be achieved.

1. Normal liver anatomy and function

The normal liver is constituted by 2 lobes, with a weight of approximately 1400-2100 g and holds approximately 13% of the body's blood supply, with a dual blood perfusion via the hepatic artery (25%) and portal vein (75%). The liver parenchyma is organized into small units (acini) that are characterized by an incoming blood supply from portal tracts (branches of liver artery and portal vein), cords of liver cells, and their intervening sinusoids, and by a peripheral outgoing blood supply (terminal liver venule). The portal tracts include a hepatic artery, portal vein branch, and a biliary duct. The low-pressure sinusoids are lined with highly fenestrated endothelial cells and flanked by plates of hepatocytes; this allows plasma to flow freely through the sinusoidal endothelial cells into the space between sinusoidal endothelium and hepatocytes, known as the space of Disse. The hepatocyte membrane is the only barrier between plasma and the hepatocytes interior.

Liver function: The liver is an essential organ, and involved in more than 500 functions, some are still not well understood. Some of the more well-known functions include bile production, production of cholesterol, protein synthesis, glycogen storage, iron storage, processing of hemoglobin, conversion of ammonia to urea, blood toxin clearance and regulation of blood coagulation.

2. Chronic viral hepatitis: epidemiology and background

Chronic hepatitis is classified according to the histopathologic grading and staging systems; grading, which varies between 0 (no activity) and 4 (severe activity), refers to the presence of various degrees of hepatocellular necrosis and inflammation, whereas staging refers to the presence of various degrees of fibrosis (stage 0 = no fibrosis), including cirrhosis as the most severe stage (stage 4). Chronic hepatitis can be caused by several etiologic factors, including autoimmune hepatitis, viral hepatitis (e.g., hepatitis B, C, D, or E), chronic drug hepatitis, Wilson's disease, alpha-1-antitrypsin deficiency disease, and non alcoholic steatohepatitis. In the US, chronic HBV (hepatitis B virus) and HCV (hepatitis C virus) infections have an estimated prevalence of 4.9% and 1.8% (1), respectively, in the general population, with a recent increase of HCV infection. Approximately 5-10% of HBV and more than 50%-80% of HCV infected individuals become chronically infected (2). Chronic viral hepatitis can lead to fibrosis, cirrhosis, portal hypertension, end-stage liver disease requiring liver transplantation, and hepatocellular carcinoma (HCC). Liver fibrosis constitutes an important cause of morbidity, mortality, and health care costs (3). Progression to cirrhosis occurs in 20% to 30% of HCV infected patients, with disease duration up to 20 years (4), and the early detection of fibrosis and cirrhosis has important clinical implications in these patients. The cumulative rates of HCC development in patients with a clinical diagnosis of HBV and HCV are 4.0%, 3.4%–7.0%, 10.5%–14.0%, and 22.4% at 3, 5, 10, and 15 years after diagnosis, respectively (5,6).

The process of transformation from chronic hepatitis to cirrhosis includes a progressive disruption of vascular anatomy and physiology. Portal blood bypasses liver parenchyma through septal venous shunts, and the parenchyma becomes more dependent on arterial blood. During this process, endothelial defenestration, deposition of collagen in the extravascular space of Disse, and formation of basal laminae occur which dramatically affect the transit time of small and large molecules. During this transformation to cirrhosis, portal

flow decreases due to increased resistance with a resultant profound effect on liver function and on the clearance of common pharmacologic agents. Under physiological conditions, alteration of portal venous blood flow is counteracted by flow changes of the hepatic artery, resulting in the maintenance of total liver blood flow (hepatic arterial buffer response), which serves not only to fulfill oxygen and metabolic demands of the liver but also to control the overall metabolic well-being of the organism by maintaining liver clearance and excretory function.

Role of liver biopsy in chronic viral hepatitis

The definitive evaluation of disease severity in chronic viral hepatitis is based on histological findings obtained by liver biopsy, used to assess the degree of fibrosis and necroinflammatory changes (7). The liver biopsy is still considered the reference standard by hepatologists, despite its limitations (morbidity, costs, and limited sampling) (8-10).

A reliable and reproducible marker of liver fibrosis and inflammation is strongly needed.

3. Current status and challenges of MRI in the evaluation of chronic hepatitis and cirrhosis

MRI is used to assess the severity of liver fibrosis, the presence of portal hypertension, cirrhosis and HCC.

Conventional MRI: Conventional MRI has a limited role in the diagnosis of fibrosis and early cirrhosis, and is mostly based on morphologic criteria, such as changes in liver morphology and different patterns of enhancement (11-14). These findings are subjective, subject to inter-observer variability, and limited in sensitivity and specificity. Detection of advanced liver fibrosis can be achieved by using double-enhanced MRI using superparamagnetic iron oxide and Gadolinium (15).

Diffusion-weighted MRI (DWI): There is data suggesting a decrease in liver ADC in liver fibrosis and cirrhosis (16-21). Restricted diffusion in liver fibrosis relies on the hypothesis that architectural distortion due to the tightly bound and proton-poor collagen fibers restricts water Brownian motion within fibrotic liver, as well as changes in perfusion associated with fibrosis (22). A recent study showed significant differences between normal and cirrhotic livers using perfusion fraction calculated with DWI (23).

DCE MRI: DCE MRI of the liver shows promising results for the estimation of diffuse liver disease and liver lesions (24-26). For example, a prior study (26) showed a correlation of estimated perfusion parameters with the severity of liver disease and the degree of portal hypertension. We also showed the potential usefulness of PWI for the prediction of advanced fibrosis and cirrhosis (27).

MR Elastography

MR elastography (MRE) is a promising technique measuring liver stiffness in chronic hepatitis (28-32), with excellent reported performance.

MR Spectroscopy

Several investigators have reported the frequencies of chemical shift from the metabolites in the liver on ¹H MRS and ³¹P MRS. For example, 80% sensitivity and specificity were achieved when using a PME/PDE ratio ≤ 0.2 to denote mild hepatitis and a corresponding ratio ≥ 0.3 to predict cirrhosis (33).

The challenges of MRI

- Improve performance of MRI for detection and characterization of HCC in cirrhosis.
- Improve the image quality of DWI, and improve ADC quantification.
- Improve spatial and temporal resolution registration correction of DCE MRI
- Need to develop automated or semi-automated image processing tools to register 3D datasets and to analyze results in terms of useful clinical parameters
- Improve SNR and spectral resolution of MRS

4. Future prospects of MRI in chronic liver disease

- Multiparametric imaging combining DWI, PWI \pm MRE
- Assess the role of high field imaging to improve spatial and temporal resolution, as well as MRS image quality.
- Assess the role of new coil systems and high parallel imaging factors.
- Develop fast MRE acquisitions.

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