Contrast-enhanced Functional Imaging of the Liver

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- The most common cause of post-operative mortality after liver resection is liver failure.
- Currently available liver function tests give limited information as global estimates.
- Contrast-enhanced hepatocyte-specific dynamic MRI offers a number of functional parameters depicting various aspects of liver function and can be calculated on a regional (for example segmental) level.

Liver function assessment

The functions of the liver are multiple and complex, including storage and synthesis, secretion and excretion, detoxification and the metabolising of nutrients, hormones and drugs. These functions are maintained by complex integrations of different cellular processes dependent on an adequate blood supply and venous drainage, a sufficient volume of healthy parenchyma and uncompromised biliary drainage. Interference with any of these components will to some extent affect liver function. It is obvious that no single test can give a comprehensive measurement of all liver functions.

Currently, methods for evaluation of liver function can be divided into three main categories:

1. Routine laboratory tests measuring surrogate markers, giving indirect indications of liver function by assessing cell permeability or damage (liver enzymes), synthetic capability (coagulation parameters and albumin) and metabolic integrity (bilirubin)(1). Most of the measured substances, however, are non-specific and serum levels are influenced by factors other than liver function.

2. Scoring systems combining laboratory and clinical information (eg, Child-Turcotte-Pugh score, Model for end-stage liver disease [MELD] and Mayo risk scores)(2-4). Most of the scoring systems were developed for a dedicated purpose, but are in clinical practice typically used for purposes not

initially intended or described.

3.Quantitative liver function tests (eg, indocyanine green [ICG] clearance,LiMAx), which measure specific aspects of function or hepatic perfusion (5).

Imaging-based liver function analysis

The principle of imaging-based functional analysis of the liver is not new. It was first applied with scintigraphyas imaging method using a number of radiopharmaceutical agents, including $^{99}Tc^{m}$-IDA, $^{99}Tc^{m}$-mebrofenin and $^{99}Tc^{m}$- galactosyl-human serum albumin (GSA)(6-8). Hepatic extraction of $^{99}Tc^{m}$-IDA and $^{99}Tc^{m}$-mebrofenin is through transport mechanisms similar to ICG and a number of scintigraphic-derived parameters have shown good correlation with ICG clearance(9).In principle functional assessment with these substrates is a clearance test using imaging sampling instead of blood sampling. Imaging-based sampling provides more accurate multi-compartmental measurements, generating data on a multitude of liver function and physiology parameters within a single examination. It also allows for analyses on a regional level that would allow clinicians to detect and account for any inhomogeneity in parenchymal function. Scintigraphic methods, however, are hampered by poor anatomical resolution compromising the accurate placement of regions of interest (ROIs).

MR functional imaging of the liver

MRI is primarily used as diagnostic modality for detection and characterization of focal liver lesions and diffuse liver disease. Furthermore, it offers excellent anatomic resolution of both vascular and biliary structures useful for treatment planning in hepatic surgery. In addition, physio-pathological information on parenchymal architecture, fibrosis, and hepatic dysfunction can be obtained by sequences enabling elastography, relaxometry, diffusion-weighted imaging (DWI), and with the use of hepatocyte-specific contrast, hepatobiliary phase imaging(10-12). Gadoxetic acid is taken up by hepatocytes using uptake and excretion receptor pathways similar to ICG and 99mTc-mebrofenin (uptake by means of organic anion-transporting polypeptide (OATP) 1B1/B3 and excretion through multi-drug resistance-associated protein 2 (MRP2))(13). A number of approaches in using gadoxetic acid-enhanced MRI to evaluate hepatic function have been pursued. In subjects with normal hepatic parenchymal and biliary function biliary enhancement is observed within 20 minutes of contrast administration. Delayed and less marked biliary enhancement has been demonstrated in cirrhotic patients (14). Decreased parenchymal enhancement is observed in patients with compromised liver function and has been described using static parameters in both quantitative and qualitative terms(15) These measurements are simple to perform and do not require additional sequences. Relative enhancement of the parenchyma has been shown to correlate with the severity of cirrhosis, ICG clearance and the risk of postoperative liver failure(16,17). Hepatic uptake of gadoxetic acid occurs over time, and a single time-point measurement may not truly reflect the enhancement profile. Dynamic hepatocyte-specific contrast-enhanced MRI is conceptually application of the dynamic scintigraphic methods in MRI. This allows the same diversity in the acquired functional parameters possible with scintigraphy, with the additional advantage of high-resolution images for much more accurate and specific sampling of vascular, hepatocyte and biliary compartments. Accurate sampling on a segmental and even sub-segmental level is possible. Acquiring multiple phases post-injection, parenchymal enhancement response over time can be constructed. With a defined input and deconvolution of curves, multiple quantitative functional parameters, including the hepatic extraction fraction (HEF; amount of contrast agent that would be eliminated in one passage through the liver) and input relative blood flow (irBF;a measure of perfusion) can be calculated (18-20).

Contrast-Enhanced Functional Imaging of the Liver in hepatic surgery

Mortality after liver resection has steadily been decreasing over recent decades, with many centres reporting post-operative mortality rates of less than 1%. Currently, the largest cause of postoperative mortality after liver resection is liver failure(21,22). To avoid these fatalities, accurate assessment of the future liver remnant (FLR) should be part of the preoperative work-up ensuring that the FLR is of sufficient volume and quality to sustain postoperative liver function and to enable regeneration. In patients with normal liver function, the FLR is assessed in terms of volume, using computed tomography (CT) or MRI(23). In patients with healthy liver parenchyma, a FLR>20% of the total estimated functional liver volume is usually sufficient. However, opinions on the minimum required FLR volume vary within the range of 15% to 40% (24). Compromised liver parenchyma in patients considered for liver resection is becoming more frequent. It is a common problem in patients with HCC, with the majority of these tumours occurring in patients with cirrhosis. With the escalating use of neo-adjuvant chemotherapy in the multimodality treatment for patients with colorectal cancer liver metastases (CRCLM), chemotherapy-associated liver injury (CALI) is increasingly encountered in this patient group. CALI has shown an association with increased morbidity, and in some cases even mortality, after resection(25). In patients with compromised parenchyma, the minimum volume of the FLR has to be increased as a function of the parenchymal damage and associated liver dysfunction(26). However, the use of preoperative liver function tests varies worldwide, and there is no consensus on the use or choice of test (24). Treatment algorithms for HCC include different combinations of liver function assessment methods, with non-uniform adoption of guideline recommendations being common (27,28). Currently used methods for assessing liver function measure global function, not considering segmental variations in function or dysfunction (ie, any reduction in liver function is assumed to be uniform throughout the parenchyma). However, in some conditions, liver function is not homogeneously distributed, with large segmental variations observed. Assessment with a global function method may over- or underestimate the functional capacity of the FLR. Overestimation may put some patients at risk for post-operative liver failure whereas underestimation may incorrectly deny some patients potentially curative surgical treatment.

MRI assessment of liver function is still evolving and requires refinement, simpification and validation. Evaluating a novel approach of function assessment in patients considered for liver surgery is complicated by the absence of a golden standard. The use of operative mortality as the endpoint in studies evaluating the clinical impact of a new method, for example function analysis, is complicated by the already low operative mortality (<1%) (29). Rather, confident extension of indications for curative-intended surgery using functional MRI assessment, with maintenance of the current low mortality rates, should be pursued.

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