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Quantification of hepatic functional capacity: a call for standardization

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Reliable assessments of liver function are becoming increasingly important as more patients with surgically amenable liver disease are considered for treatment. Static markers of liver function are not sufficient to provide accurate assessments of hepatic function in order to risk stratify patients undergoing hepatic resection. Metabolic tests are dynamic indicators of liver function, but can be unreliable under certain conditions and thus difficult to make comparisons. Clearance tests avoid some of the pitfalls encountered during metabolic testing, but depend on hepatic blood flow and say little about hepatocyte function. Testing that combines imaging with measures of hepatocyte uptake may offer the most utility when planning surgical resections.

Reliable assessment of hepatic functional capacity is becoming increasingly important as outcomes of hepatic resection and transplantation continue to improve and the medical field continues to push the boundaries of patient care. As indications for surgical intervention expand, precise knowledge of liver function becomes crucial to the appropriate selection of patients. While volumetric measurements provide precise anatomic information of liver segments, they cannot account for underlying function. Likewise, optimization of allograft utilization, especially for grafts from extended criteria donors, necessitates reliable, objective metrics of liver function. While clinical assessment by experienced surgeons remains the gold standard for evaluating the quality of potential allografts, regional sharing may limit this practice in the future. Simple means will no longer be sufficient as we aim to reach more patients while maintaining the highest clinical standards.

With its many functions, the liver has traditionally been difficult to assess by non-invasive means. Its anatomic features can be evaluated grossly or histologically. Neither, however, provides functional information and both are subject to inter-observer variability. Biochemical profiles of liver function are objective, but static and subject to confounding in the acute setting. Additionally, they are all indirect markers of hepatic function. A number of dynamic tests of liver function have emerged recently and aim to provide objective, reliable and simple means of assessing parenchymal liver function and hepatic reserve.

Quantitative testing of dynamic liver function measures the capacity of the liver to uptake, metabolize and clear a number of substances. Multiple methods of detection and quantification of these activities have been utilized over the last four decades. Clinical utilization of these methods depends on their reliability and the ease of testing. Whereas some rely on cumbersome, inaccessible equipment, others are portable and easy to use.

Metabolite testing

Hepatic breath testing was among the first dynamic tests of liver function. In these tests, substances metabolized primarily in the liver, are labeled with carbon isotopes ^{13}C or ^{14}C and administered either orally or parenterally. Following hepatic uptake and metabolism, the labeled CO_2 diffuses into the systemic circulation and is collected through exhalation. The concentration of radiolabeled carbon is then

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determined by mass or infrared spectrometry. Given the low natural occurrence of these isotopes, any appreciable increase is thought to directly reflect hepatic enzyme activity.

Several substrates have been utilized in hepatic breath tests. Aminopyrine was one of the first breath tests developed to estimate hepatic functional mass. Formaldehyde is generated from aminopyrine through a 2-step metabolic pathway and then oxidized to bicarbonate and exhaled as CO_2. Following administration, serial breath samples are obtained every 30 min for 3 h. This method evaluates the P450 system and has been utilized to stratify patients with various degrees of liver dysfunction.[1] Additionally, there have been reports to suggest aminopyrine breath tests (ABT) are more predictive of recovery in patients with alcoholic hepatitis than standard biochemical profiles.[2] However, ABTs are unable to discriminate between intermediate stages of fibrosis. Their accuracy is further compromised in cholestatic liver diseases because of the lack of a biliary phase. Variations in P450 N-demethylation activity because of subject age, gender or concomitant medications also limit the accuracy of this test. Furthermore, concerns about agranulocytosis have limited widespread use of ABTs .[3]

Methacetin is an alternative substrate for hepatic breath testing with a more favorable side effect profile than ABT. Its metabolism by the CYP1A2 system forms acetaminophen and CO_2. Whereas ABT is unaffected by hepatic blood flow, the methacetin breath test (MBT) is quite sensitive to blood flow and subject to "first-pass" effects by the liver. Stockmann *et al.* prospectively used a technical variant of the MBT called LiMAx in post-hepatectomy patients.[4] LiMAx significantly correlated with residual liver volume and was the only predictor of liver failure and mortality on multivariate analysis in their study. They also demonstrated an ability to predict remnant liver function capacity preoperatively by combining LiMAx results with CT volumetry. Individual genetic polymorphisms in enzymes responsible for metabolism of substrates utilized in the LiMAx test may complicate the interpretation of results between individuals.

Utilizing complex metabolic pathways, the methionine breath test (MeBT) allows for specialized testing of hepatic mitochondrial function.[5] Following administration of ^{13}C-labeled methionine, a multi-step pathway yields α-ketobutyrate and $^{13}CO_2$. One caveat to consider is that laboratories employ different isomers of labeled methionine and methods of administration, which makes comparisons of results difficult.

While hepatic breath testing offers a dynamic assessment of liver function, reliability is of concern and results may depend on the serum kinetics of bicarbonate pools. Basal CO_2 levels are not static and fluctuate depending on an individual's overall metabolic state. Additionally, genetic polymorphisms of enzymatic machinery make comparisons among individuals challenging. These discrepancies warrant consideration when interpreting breath testing results.

Alternative dynamic methods of hepatic functional testing rely on the clearance of substances metabolized primarily in the liver. Galactose clearance has been shown to reliably estimate hepatic functional mass.[6] Following parenteral administration, serum samples are obtained to calculate the rate of galactose clearance. While rarely abnormal in cases of biliary obstruction, it is markedly reduced in cases of cirrhosis and has prognostic value in patients with acetaminophen-induced liver toxicity.[6,7] Similarly, elimination of cholate following administration in patients with early, compensated cirrhosis has been helpful in predicting those with marked functional impairment who are at most risk for decompensation.[8]

Caffeine clearance is an alternative measure of hepatic functional reserve. Following ingestion of caffeine, levels can be obtained serially in either blood or saliva. The utility is similar to other hepatic clearance tests. There is an age-dependent decrease in hepatic metabolism of caffeine, whereas smoking increases caffeine clearance.[9]

Metabolite formation has shown promise as a dynamic test of hepatic reserve. Lidocaine is preferentially metabolized by the hepatic cytochrome P450 system into monoethylglycinexylidide (MEGX). Serum samples are drawn 15 min after parenteral administration of lidocaine and measured using an immunoassay. Higher concentrations of MEGX have been associated with improved survival in patients with cirrhosis, whereas a decline in levels correlated with worsening histology in chronic hepatitis.[10,11]

Dye clearance

Other tests of hepatic functional capacity directly measure the excretory capacity of the liver. Introduced in the year 1924, bromsulphthalein (BSP) was one of the first dye tests. Following injection, BSP binds to albumin and is rapidly taken up by hepatocytes.[12] Rate of BSP uptake, storage and excretion can be measured as a surrogate for hepatic functional capacity.

An alternative dye used with greater frequency is indocyanine green (ICG). Its advantages include a higher hepatic extraction ratio. Additionally, ICG can be measured directly by spectrophotometry or continuously with a fingertip optical sensor.[13] This test overcomes the cumbersome equipment needed in other dynamic functional tests and has been shown to be proportional to liver parenchymal cell volume.[14] Not only is ICG clearance invaluable for planning surgical resections, it can also give real-time information intra-operatively. Pulse spectrophotometry measurements of ICG taken after trial clamping accurately predicted post-resection liver volume, this correlates with outcome.[15,16]

Given the ease of use and portability of testing, ICG testing has a key role in the area of transplantation. As the gap between graft supply and need continues to widen, donor utilization will necessitate reliable markers of quality in order to minimize recipient risk. Visual inspection will become increasingly difficult as organs are increasingly shared among the region. ICG testing offers accurate and reliable results that can be easily obtained. Results from 53 adult brain-dead donors showed ICG–plasma disappearance rate correlation with graft function and outcome.[17] It was the only donor variable that was associated with 7 day graft survival. Limitations of ICG testing include a dependence on hepatic blood flow.

Whereas metabolite and breath testing evaluate hepatic metabolic function, elimination tests are unable to truly differentiate

blood flow from cell function. While this is a limitation in assessing hepatic functional capacity, it lends itself to estimating hepatic blood flow when administration reaches a steady state.[18]

Imaging based

When combined with functional testing, image based testing can help predict the hepatic reserve prior to hepatectomy. This is important especially in the neoadjuvant setting where the remnant liver may be diseased. The level of expression of receptors for galactosyl human serum albumin (GSA) strongly correlates with liver function.[19] Following injection with ^{99m}Tc-GSA, hepatocyte uptake depends on functional mass. Utilizing single-photon emission computed tomography, assessment of both liver function and volume can be made at the same time. These tests can be particularly useful when the liver is not homogeneous, such as in conditions as unilateral cholestasis or after portal vein embolization. An alternative approach utilizes gadoxetic acid-enhanced MR to assess hepatic function. Following injection of gadoxetic acid, approximately 50% of the contrast agent is taken up by hepatocytes and excreted into the biliary system. In one retrospective study, the degree of enhancement on MR was inversely related to the probability of liver failure.[20] Further prospective studies are needed for validation, but may provide yet another tool to preoperatively risk stratify patients undergoing major hepatic resection.

Conclusion

Accurate assessment of liver function requires dynamic measurements of the capacity of the liver to take up, metabolize and excrete substances. This information is important in liver surgery, as well as to assess the suitability of organs for transplantation. Static means are inadequate for measuring hepatic functional reserve. While several methods are available, dye clearance is emerging as one of the more practical tests with broad clinical applications. It provides accurate, objective measurements in real-time that are easily reproducible. Its role will continue to be defined as more research is conducted.

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References

1. Reichen J, Jürg R. Assessment of hepatic function with xenobiotics. Semin Liver Dis. 1995;15(03):189–201.
2. Giannini EG, et al. 13C-galactose breath test and 13C-aminopyrine breath test for the study of liver function in chronic liver disease. - PubMed - NCBI [Internet]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15765448.
3. Miele L, Marrone G, Cefalo C, et al. Potential use of liver function breath tests in the clinical practice. Eur Rev Med Pharmacol Sci. 2013;17(Suppl 2):82–89.
4. Stockmann M, Lock JF, Riecke B, et al. Prediction of postoperative outcome after hepatectomy with a new bedside test for maximal liver function capacity. Ann Surg. 2009;250(1):119–125.
5. Grattagliano I, Ignazio G, Lauterburg BH, et al. 13C-breath tests for clinical investigation of liver mitochondrial function. Eur J Clin Invest. 2010;40(9):843–850.
6. Tygstrup N. Determination of the hepatic elimination capacity (Lm) of galactose by single injection. Scand J Clin Lab Invest Suppl. 1966;18:118–125.
7. Schmidt LE, Ott P, Tygstrup N. Galactose elimination capacity as a prognostic marker in patients with severe acetaminophen-induced hepatotoxicity: 10 years' experience. Clin Gastroenterol Hepatol. 2004;2(5):418–424.
8. Shrestha R, McKinley C, Showalter R, et al. Quantitative liver function tests define the functional severity of liver disease in early-stage cirrhosis. Liver Transpl Surg. 1997;3(2):166–173.
9. Joeres R, Klinker H, Heusler H, et al. Influence of smoking on caffeine elimination in healthy volunteers and in patients with alcoholic liver cirrhosis. Hepatology. 1988;8(3):575–579.
10. Huang YS, Lee SD, Deng JF, et al. Measuring lidocaine metabolite–monoethylglycinexylidide as a quantitative index of hepatic function in adults with chronic hepatitis and cirrhosis. J Hepatol. 1993;19(1):140–147.
11. Shiffman ML, Luketic VA, Sanyal AJ, et al. Hepatic lidocaine metabolism and liver histology in patients with chronic hepatitis and cirrhosis. Hepatology. 1994;19(4):933–940.
12. Baker KJ. Binding of sulfobromophthalein (BSP) sodium and indocyanine green (ICG) by plasma alpha-1 lipoproteins. Proc Soc Exp Biol Med. 1966;122(4):957–963.
13. Shimizu S, Kamiike W, Hatanaka N, et al. New method for measuring ICG Rmax with a clearance meter. World J Surg. 1995;19:113–118.
14. Hashimoto M, Masaji H, Goro W. Hepatic parenchymal cell volume and the indocyanine green tolerance test. J Surg Res. 2000;92(2):222–227.
15. Thomas MN, Weninger E, Angele M, et al. Intraoperative simulation of remnant liver function during anatomic liver resection with indocyanine green clearance (LiMON) measurements. Hpb. 2015;17(6):471–476.
16. Garcea G, Ong SL, Maddern GJ. Predicting liver failure following major hepatectomy. Dig Liver Dis. 2009;41(11):798–806.
17. Zarrinpar A, Lee C, Noguchi E, et al. A rapid, reproducible, noninvasive predictor of liver graft survival. J Surg Res. 2015;197(1):183–190.
18. Bircher J. Quantitative assessment of deranged hepatic function: a missed opportunity? Semin Liver Dis. 1983;3(4):275–284.
19. Ge P-L, Du S-D, Mao Y-L. Advances in preoperative assessment of liver function. Hepatobiliary Pancreat Dis Int. 2014;13(4):361–370.
20. Wibmer A, Prusa AM, Nolz R, et al. Liver failure after major liver resection: risk assessment by using preoperative gadoxetic acid-enhanced 3-T MR imaging. Radiology. 2013;269(3):777–786.