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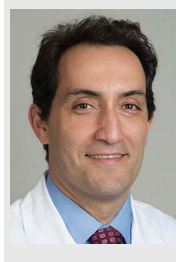
Portable device for the analysis of liver function: a boon to liver surgery and critical care

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Liver biology, liver disease and its management present a myriad of challenges to clinicians. Difficulties arise in determining liver functional capacity, which must be effectively measured in a quantitative reproducible manner. Measurement of indocyanine green (ICG) clearance, an exceptional tool that has been used for decades to assess liver function, has traditionally been cumbersome to perform. New technology now allows for rapid and noninvasive determination of ICG clearance making it clinically accessible. This adds ICG clearance measurement to the armamentarium of physiologic monitors that could be routinely used in the evaluation of patients undergoing liver surgery or in the intensive care setting.

Despite significant advances made in liver transplantation and liver surgery, assessing resectability, donor graft quality and post-resection liver function remain formidable obstacles. The indocyanine green plasma disappearance rate (ICG-PDR) test is a widely used quantitative measure of liver function. ICG is a water-soluble, inert compound. Following intravenous injection, it distributes uniformly in the blood within 2–3 min, binding to albumin, α 1-lipoproteins and β -lipoproteins. ICG is then selectively taken up by hepatocytes and excreted into the bile without significant extrahepatic elimination or enterohepatic recirculation.[1,2] Therefore, ICG clearance reflects several important physiological parameters, including hepatic blood flow and hepatocellular function.[3]

A noninvasive liver function monitoring system, the LiMON[®] (Pulsion Medical Systems, Munich, Germany), has been developed that measures ICG elimination by pulse spectrophotometry, making this assay much more accessible. This is a rapid, reproducible and

noninvasive technique that allows bedside assessment of ICG-PDR (%/min) and ICG retention after 15 min (R15, %). [4] Given the wide range of clinical applications, ease of use and prognostic value, this is an invaluable clinical tool. Here, we review its potential utility in liver resection, transplantation and critical care.

Liver surgery

Liver resection is a mainstay in the treatment of primary and secondary liver malignancies. A major limitation is prediction of an adequate functional liver remnant after resection. This is especially complicated in hepatocellular carcinoma, as these malignancies typically arise in a background of preexisting liver disease where the functional capacity is impaired. Therefore, accurate preoperative assessment of liver function is a prerequisite to major hepatectomy for prevention of post-hepatectomy liver failure. Generally accepted safe resection limits require a liver remnant of 20–30% of normal liver and 30–40% or greater of diseased

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liver.[5] Standard preoperative planning consists of liver volumetry combined with conventional testing and scoring systems (e.g., aspartate transaminase, alanine transaminase, international normalized ratio, bilirubin, Child score or Model for End-stage Liver Disease [MELD]) to estimate functional reserve. These methods are static tests hampered by the inability to yield functional information.

ICG-PDR provides an excellent functional assessment of the liver and has been shown to be proportional to liver parenchymal cell volume as assessed by CT, making ICG clearance invaluable for estimating the extent of resection.[6,7] Furthermore, numerous studies have found ICG elimination can predict liver dysfunction and mortality following hepatectomy.[8] For example, in a study of 127 patients undergoing liver resection, Lau et al. found ICG clearance ($R_{15} > 14\%$) to be the best test to predict post-resection mortality.[9] More recently, ICG clearance has been used to assess liver remnant function intraoperatively in real time. Liver function was measured using ICG clearance by pulse spectrophotometry and ICG-PDR measurements were taken after trial clamping of arterial and portovenous inflow of the resected segments. The results showed that post-resection liver volume could be accurately predicted by trial clamping of liver inflow and simulated post-resection liver function and post-hepatectomy liver failure.[10] Indeed, low ICG-PDR rates post-hepatectomy are associated with poor prognosis, increased postoperative complications, and increased morbidity and mortality.[8]

Liver transplantation

Living donor liver transplantation

One of the more promising areas for incorporating ICG technology is in transplantation. The preparation for living donor liver transplantation (LDLT) is complex and a key component is appropriate donor selection. The donor must be able to safely undergo the operation and retain an adequate hepatic mass while also providing a suitable graft volume for the recipient.

LDLT grafts carry a higher risk of complications, including delayed graft function and early graft loss. Thus, reliable evaluation of graft function is crucial after LDLT. In one study of 30 adult recipients up to 28 days after LDLT, ICG elimination rates were found to correlate well with both liver scintigraphy and histopathology. Elimination rates after LDLT in recipients with good graft function were maintained and were significantly different from rates in recipients without good graft function. In fact, there were already significant differences in ICG levels 24 h after LDLT. Poor ICG clearance in patients without good outcomes is thought to reflect a suboptimal hemodynamic state that impedes effective hepatic blood flow and liver regeneration after LDLT. The authors concluded that ICG values can predict clinical outcomes in the early postoperative period after LDLT by rapidly reflecting the influence of systemic dynamics on splanchnic circulation.[11] A more recent retrospective study of 178 patients after LDLT found ICG clearance on postoperative day 3 to be the strongest predictor of early graft failure

within 3 months with a sensitivity of 100% and specificity of 97%.[12] ICG elimination rate has also been shown in a study of 49 adult LDLT recipients to identify grafts at risk for small-for-size syndrome.[13]

Deceased donor liver transplantation

Deceased donors are the primary source of organs for liver transplantation in the United States. However, the waiting list for transplantation continues to grow as the donor pool has stagnated. To combat this phenomenon, the use of extended criteria grafts has been expanded. Assessment of graft quality has largely relied upon visual inspection by the procuring surgeon with or without the use of liver biopsy. Liver biopsy can be time-consuming and is not always readily available. Optimizing the use of extended criteria grafts while minimizing recipient risk requires accurate and reproducible assessment of graft quality. In a study of 53 adult brain-dead donors, ICG-PDR measurements were performed before organ procurement. The results were compared with graft function and outcomes. ICG-PDR was the only donor variable to be significantly associated with 7-day graft survival.[4] In principle, this method would allow for standardization of graft quality assessment and lead to increased utilization of organs.

Posttransplant graft dysfunction

After transplantation, the goal shifts toward prevention of post-transplant complications. Early identification of delayed graft function is essential for rapid intervention. ICG-PDR levels measured as early as 1 h post-reperfusion or within the first 24 h after reperfusion have been found to be strongly associated with initial graft dysfunction. Survival too appears to be significantly lower in patients with low ICG-PDR.[14] Another study evaluated ICG-PDR measurements in 86 patients for 7 days after deceased donor liver transplantation. There ICG-PDR was significantly different in patients who suffered postoperative complications, graft loss or death.[15] Yet another way in which ICG-PDR can aid in the early detection of graft problems is in diagnosing and following hepatic artery thrombosis.[16]

Critical care

Multisystem organ failure remains the most frequent cause of death in the critically ill. ICG-PDR has been found to be highly correlated with outcomes in these patients.[17] Sakka et al. compared the prognostic value of ICG-PDR in critically ill patients to standard ICU scoring systems. Critically ill patients admitted to the ICU were scored according to Simplified Acute Physiology Score II and APACHE II. ICG-PDR was measured and found to be significantly lower in nonsurvivors independent of diagnosis, whether it was sepsis, acute respiratory distress syndrome or other causes. Mortality was 80% in patients with ICG-PDR $< 8\%/min$ compared to 20% in patients with ICG-PDR $> 16\%/min$. The prognostic properties of ICG-PDR as a singular parameter predicting survival was comparable to Simplified Acute Physiology Score II and superior to APACHE II. Areas under the curve

(AUCs) were 0.745, 0.755 and 0.680, respectively.[17] Inal et al. found that ICG-PDR cutoff of 14.6 led to sensitivity of 77.8, specificity of 72.7 and AUC of 0.765, much better than APACHE II, where a cutoff of 24 led to a sensitivity of 66.7%, specificity of 77.3% and AUC of 0.692.[18]

ICG-PDR has also been used to predict outcomes in patients presenting with acute liver failure. Measured at admission, ICG-PDR was significantly lower in patients not recovering spontaneously. ICG-PDR < 6.3%/min on day 1 predicted death or transplantation with a sensitivity of 85.7% and a specificity of 88.9%. ICG-PDR < 5.3%/min at any time predicted death or transplantation with a sensitivity of 85.7% and specificity of 66.7%.[19] ICG-PDR has also been investigated as a predictor of survival in end-stage liver disease to increase prognostic accuracy of the MELD score. Although MELD has been shown to be superior to ICG-PDR for estimation of survival in patients with decompensated cirrhosis, a combined system, the MELD-ICG, was found to be more accurate in predicting survival in intermediate to advanced cirrhosis than the MELD alone in a study with 321 patients. Combination of ICG half-life with MELD led to better discrimination in patients with intermediate to advanced cirrhosis with an MELD score between 10 and 30.[20]

Summary

Complications arising from liver failure and after liver transplantation or resection result in significant morbidity and mortality. An accurate assessment of liver function is a key component of the clinical management of these patients. Ideally, assessment of liver function should include both

anatomical information and functional evaluation of the whole and partial liver, providing reliable information for accurate assessment of surgical risks. Traditional measures of liver function are static tests, such as liver enzymes, markers of protein synthesis in the liver and bilirubin. Dynamic testing, on the other hand, considers the complexity of liver functions and reveals otherwise hidden hepatocellular dysfunction. ICG testing is a valuable tool for this purpose. New technology using pulse dye densitometry with near-infrared wavelength finger clip sensor greatly facilitates measuring ICG-PDR. Although the sensitivity and specificity of ICG-PDR are not high enough to allow the use as a stand-alone test, in conjunction with other testing, it greatly improves the estimation of liver function and has the advantage of being performed noninvasively at the bedside and providing results within a few minutes.

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