ICG Clearance Monitoring in ICU Patients

E. Levesque and F. Saliba

Introduction

Indocyanine green (ICG) clearance has been used, since the 1950s, as an indicator of dynamic liver function. The emergence of static liver function tests together with imaging and histology, has reduced the use of ICG measurements in the clinical setting. During the last two decades, methods to assess the hepatosplanchnic circulation and liver function have been the focus of intense investigation. The monitoring of this regional circulation has been shown to be the best predictor of outcome in critically ill patients [1]. As technologies advance, two mains goals can be identified concerning hemodynamic monitoring: The first is to make measurements using non-invasive tools in order to eliminate the risks associated with invasive monitoring; the second is to find a single measurement that could predict patient status. The same points are currently needed in regional hemodynamic monitoring. This chapter briefly considers ICG clearance physiology and its various methods of measurement, reviews the indications for ICG clearance measurement, and defines the current interests and limits of this technique with regard to hepatic functional impairment in critically ill patients with sepsis, liver disease, or after major hepatic surgery and liver transplantation.

Physiology of Indocyanine Green

ICG is a water-soluble, nontoxic tricarbocyanine dye. The active substance or dyestuff, ICG, is the mono-sodium salt of 1-[sulfobutyl] 3.3 dimethyl 2 {7 [(4 sulfo butyl) 3.3 dimethyl 4.5 benzoindoliny liden (2)] heptatrien(1.3.5) yl} 4.5. benzoindolium iodide. Its molecular formula is $C_{43}H_{47}N_2NaO_6S_2$, and its molecular weight is 774.97 Da.

The principal characteristic of ICG is that it is extracted nearly exclusively by the hepatic parenchymal cells and excreted almost entirely into the bile without enterohepatic circulation [2]. Indeed, after injection, ICG binds almost completely, within 1–2 seconds, to plasma proteins (globulin, α_1-lipoproteins) without extravascular distribution. It is taken up by the parenchymal cells of the liver, bound by acceptor proteins, and then, through the hepatic cells, excreted via the canalicular membrane and eliminated with the bile in unchanged form. ICG is detectable 15 minutes after injection into the bile, with a maximum concentration from 1/2 to 2 hours after injection, depending on the amount injected. The kinetic of ICG plasma disappearance has been thoroughly described in previous articles [3, 4]. Because of its metabolism, the ICG elimination rate, a dynamic test, has been largely used to assess liver function, hepatic blood flow, and hepatosplanchnic hemodynamics [5–7].

ICG is, in general, very well tolerated and safe. In all of the reported studies using ICG, no side-effect has been related to its use. However, in patients with an iodine allergy or thyrotoxicosis, use of ICG is not advised, since it contains iodine. ICG injection can, in extremely rare cases, cause nausea and an anaphylactic reaction (incidence of approximately 1:40000) with the main manifestations being pruritus, urticaria, tachycardia, hypotension, dyspnea, and shortness of breath.

Principles of Measurement

Various techniques (invasive and non-invasive) are available to evaluate ICG elimination after an intravenous injection. These methods give us various derived values that quantify ICG elimination: the clearance (Cl-ICG), the plasma disappearance rate (PDR-ICG), which is the percentage of ICG eliminated in 1 minute after an ICG bolus, and the retention rate at 15 minutes (R15) (**Table 1**).

Invasive Methods

Spectrophotometric concentration analysis at regular time intervals on serial blood samples was the first method described and remains the gold standard. To decrease the number of blood samplings, which are cost- and time-consuming, the insertion of a fiber-optic aortic catheter into the femoral artery has been proposed (COLD-System Z_{021}, Pulsion Medical Systems, Munich, Germany). Currently, because of its invasiveness, its use is limited to experimental settings.

Non-Invasive Methods

For 10 years now, ICG elimination can also be determined non-invasively by a measure based on spectrophotometry. The patient is monitored with an ICG finger clip, which is connected to a liver function monitor (LiMON®, Pulsion Medical System, Munich, Germany) via an optical probe. After injection, ICG is detected from fractional pulsatile changes in optical absorption. The optical peak absorptions of 805 nm and 890 nm allow continuous measurements of PDR-ICG. For each measure, a 0.25 to 0.5 mg/kg bolus of ICG is injected through a peripheral or central venous catheter and immediately flushed with 10 ml of normal saline. Administration is always performed after dilution of the lyophilisate in 10 ml of accompanying solvent or ice-cold 5 % dextrose, in order to obtain a concentration of 2.5 mg/ml. The dose administered per patient is calculated from the weight of the patient on the basis of 0.25 to 0.5 mg/kg. Sakka et al. showed that a dosage of ICG of 0.25 mg/kg appeared to be more accurate for transcutaneous measures of PDR-ICG than a 0.5 mg/kg bolus in critically ill patients ($r = 0.95$, $p < 0.0001$, with a mean bias 1.0 ± 2.5 %/min) [8]. The monitor

Table 1. Parameters that quantify indocyanine green (ICG) elimination

Parameter	Calculation	Normal range	Unit
Plasma disappearance rate of ICG (PDR-ICG)	$\ln 2/t_{1/2} \times 100$	18–25	%/min
ICG clearance	$Vd_{circ} \times PDR$	500–750	ml/min
ICG retention rate after 15 min	$[ICG_{t=15}] / [ICG_{t=0}] \times 100$	0–10	%

Vd_{circ}: volume of distribution of the dye

then determines automatically the PDR-ICG by a mono-exponential transformation of the original ICG concentration curve and backward extrapolation to the time point 'zero' (100 %), describing the decay as the percentage of change per time.

With this non-invasive monitoring, the ICG elimination is determined without any time delay, (the results being obtained within a few minutes, depending on the circulation time). This can be done at the bedside and reduces the number of blood samples. Recently, several studies have reported a good correlation between invasive and non-invasive methods [9–14]. A good correlation between invasive and non-invasive techniques (r^2: 0.81 to 0.97) has been reported in different clinical settings, i.e., critically ill patients [13], patients awaiting liver transplantation, liver transplanted patients [10, 12, 14], and patients being assessed for suitability of hepatic resection [9]. However, von Spiegel et al. [12], in 9 patients undergoing liver transplantation, observed that the PDR-ICG values measured by the non-invasive method tended to be relatively lower than the invasive Cl-ICG. This difference is linked, in these patients, to an increase in the volume of distribution (Vd_{circ}) of ICG just after the surgery. The pulse dye densitometry method for assessing liver function and hepatic blood flow can be used in hemodynamically stable and unstable patients [11]. However, the PDR-ICG value should be interpreted with caution in some situations.

Limits of ICG Pharmacokinetics Interpretation

The moment in the course of the day when ICG measurements are obtained is important. Indeed, circadian variations in hepatic blood flow and in ICG kinetics have been observed in healthy male volunteers [15]. The plasma clearance of ICG was lowest at 14:00 and highest during the night. Two previous studies have shown that several factors (postural change and exercise [16], food [17], drugs, such as angiotensin converting enzyme inhibitors [18] or N-acetylcysteine [19]) modify liver blood flow and ICG clearance. Physiologically, it has been shown that the volume of distribution of ICG is distributed in the vascular bed and is equal to the plasma volume assessed by [^{131}I]-labeled albumin [6].

The Current Place of ICG in Clinical Practice (Table 2)

Prognostic Marker in the Intensive Care Unit

Several prognostic scores have been tested and validated in intensive care patients. In many of these (Simplified Acute Physiology Score [SAPS] II, Sequential Organ Failure Assessment [SOFA]...], bilirubin is the only variable used to assess liver function and hepatosplanchnic blood flow. Yet, Sakka et al. have shown that the ICG-PDR on admission to the intensive care unit (ICU) was as sensible as other scores, such as APACHE II or SAPS II [20]. In their study, in 336 patients admitted to the ICU, PDR-ICG was as sensible as and more specific than bilirubin (area under the curve [AUC] 0.831 for PDR-ICG, with a cut-off point ≤ 10.3 %/min versus AUC 0.782 for bilirubin ($p < 0.06$), using receiver operating characteristic [ROC] curves) [21]. Gottlieb et al. [22] also observed, in seven injured patients with hepatic venous catheters, an earlier decrease in ICG clearance compared to bilirubin in cases of liver dysfunction. They concluded that ICG clearance was more sensitive than bilirubin for detecting liver dysfunction [22]. Similar results have been obtained in subgroups

Table 2. Current use of indocyanine green clearance (ICG) monitoring

In the intensive care unit	• Prognostic markers (in critically ill patients, in septic shock) • Assessment of hepato-splanchnic hemodynamics
In hepatology	• Assessment of liver functional reserve in cirrhosis • Prognostic value in cirrhosis
In surgery	• Evaluate hepatic functional reserve before liver resection • Predict mortality and morbidity after surgery (liver resection, thoracic surgery, cardiac surgery) • To use in decision trees to select the surgical procedures in patients with impaired liver functional reserve
In liver transplantation (LT)	• Before LT: for selection of the graft • During LT: inform about the graft reperfusion • After LT: evaluate graft function and identify early graft dysfunction, predict graft and patient outcome, help to diagnose hepatic artery thrombosis and acute rejection.

of critically ill patients. In surgical critically ill patients, the plasma clearance rate of ICG was higher in survivors compared to non-survivors (11.1 ± 7.1 % versus 4.8 ± 4.3 %) [23]. In another study in 42 patients with trauma or shock, PDR-ICG predicted survival (15.0 ± 6.9 %/min in the survivors vs. 6.6 ± 5.0 %/min in non-survivors) whereas total bilirubin, alkaline phosphatase, and serum glutamic-oxalacetic transaminase, were identical in the two groups [24].

In patients with septic shock, the ICG elimination rate is an indicator of hepatocellular dysfunction; indeed, in a recent article, Kimura et al. reported an association between hepatocellular injury and a reduction in hepatic ICG clearance [25]. Moreover, in patients with septic shock, Kimura et al. showed that sequential changes in the elimination rate of ICG could predict survival. When the Cl-ICG increased, from 24 to 120 hours after the onset of the septic shock, it was associated with a good outcome; however, when the Cl-ICG remained stable or decreased, the patients died [25]. Knowing that regional variables are more important predictors of mortality compared with global volume-related hemodynamic [1], the PDR-ICG appears to be a very useful tool in the ICU. It is an excellent test to estimate hepatosplanchnic blood flow in patients with hemodynamic shock, and can be used as a prognostic factor on admission to the ICU.

Hepatosplanchnic Hemodynamics In Different Clinical Settings

Multiple organ failure syndrome is a major cause of death in patients in the ICU. It is associated with hepatosplanchnic hypoperfusion leading to an inadequate perfusion of the gut and damage to the mucosa of the intestine. This could result in a loss of its barrier function and lead to translocation of bacteria or endothelin into the circulation. After surgical interventions, the incidence of hepatosplanchnic hypoperfusion ranges from 1 to 2 %, depending on hemodynamic disturbances, with the same consequences as in septic shock.

The PDR-ICG (non-invasive method) has been validated as a marker of hepatosplanchnic perfusion [20, 26]. Several authors have used the PDR-ICG to evaluate the effects of treatments on the hepatosplanchnic circulation. After surgery, the PDR-ICG has been used to select patients at risk of hepatosplanchnic hypoperfusion and

to guide therapy or to decide when to use more invasive devices to monitor this perfusion [27]. For example, in patients with septic shock, in whom the ICG clearance is predictive of survival, Lehmann et al. showed an increase in PDR-ICG after prostaglandin (PGI2 analog – Iloprost) administration and a protective effect of this drug on the hepatosplanchnic circulation [26]. The same results were observed with dopexamine with a positive effect on the PDR-ICG [27].

In another setting, the PDR-ICG has been largely used to evaluate the ventilator effect of positive end-expiratory pressure (PEEP) on venous return, thus altering systemic hemodynamic patterns and hepatosplanchnic blood flow. It was shown that PEEP decreased venous return and modified splanchnic hemodynamics in an experimental setting. However, in patients after orthotopic liver transplantation, in spite of the increase in the PEEP (from 0 to 10 cmH_2O) and deterioration of cardiac flow in half the patients, the PDR-ICG remained normal and stable [29]. After cardiac surgery, with the same PEEP level, the PDR-ICG remained unchanged [30].

In chronic intestinal ischemia [31] and during abdominal compartment syndrome [32, 33], ICG clearance was used to evaluate the effect on hepatosplanchnic hemodynamics of increasing cardiac output by fluid loading. The limitation of these studies is the lack of evaluation of the ICG distribution volume.

Cirrhosis

ICG clearance is thought to be adequate as an estimate of liver functional reserve in patients with cirrhosis and to reflect the degree of sinusoidal capillarization, portovenous shunt, and modifications in liver blood flow [4]. In cirrhotic patients, ICG clearance is significantly lower than in healthy patients, mainly with an intrinsic decrease of ICG hepatic uptake [34]. Indeed, the liver parenchymal cell volume in cirrhotic patients (874 ± 161 ml) was significantly smaller that in patients without cirrhosis (1284 ± 352 ml) [35]; the parenchymal cell volume per body weight was significantly correlated to ICG clearance.

Few data are available on ICG clearance and its prognostic value in cirrhotic patients. In a series of 102 cirrhotic patients (cirrhosis of various etiologies), the PDR-ICG was correlated with the Child-Pugh score [36]. Similarly, Herold et al., in patients with hepatitis C virus cirrhosis, reported an inverse correlation between several quantitative tests of liver function with ICG clearance and the Child-Pugh score [37]. In this study, patients with Child-Pugh A had an ICG clearance (0.15 ± 0.05 l/min) at the lower limit of normal; in patients with Child-Pugh B and Child Pugh C, the ICG clearance was significantly lower (0.07 ± 0.04 l/min and 0.03 ± 0.02 l/min, respectively).

During the follow-up of cirrhotic patients, ICG has been used as a predictor of survival [38]. In this study, 105 cirrhotic patients were followed for an average of 31 months, with 38 deaths over this period. The probability of survival was lower in patients with an ICG clearance less than 300 ml/min (70 %), than in patients with an ICG clearance greater than 1000 ml/min (80 %). However, among the covariates, ICG clearance was not independently associated with survival [38].

In a prospective study, Oellerich et al. [39] suggested that dynamic liver function tests such as Cl-ICG were superior to conventional liver function tests in assessing short-term prognosis in cirrhotic patients [39]. In this study, 107 adult candidates for liver transplantation were included; 18 died in the 120 days following inclusion. The patients who survived for at least 120 days showed a significantly lower ICG half-life compared to non-survivors (24.5 vs 12.3 min).

Major Hepatic Surgery

Post-operative hepatic failure is a life threatening complication that occurs in 1 to 5 % of hepatic resections. Evaluating the hepatic functional reserve is essential before surgery in order to limit the risk of post-operative hepatic failure. Thus, to predict mortality and morbidity after liver resection, several authors have used ICG clearance in addition to imaging and volumetric assessment [40, 41].

Nonami et al. [42] examined various predictive factors in 315 patients over 11 years. In this study, there were 291 survivors and 24 patients with post-operative liver failure. Among the factors studied, ICG clearance and blood loss during surgery were the only factors independently correlated to survival. Similarly, Lau et al. [43], in a series of 127 patients, reported cut-off values for ICG retention rate at 15 minutes of 14 % for major hepatectomy and 23 % for minor hepatectomy. The relative risk of death for major hepatectomy was 3 if the ICG retention rate at 15 min exceeded the cut-off [43]. For Hemming et al. [44], neither age nor standard liver function tests were useful as preoperative prognostic indicators of survival; only ICG clearance was a significant marker in determining outcome. According to the authors [44], below the cut-off point of 5.2 ml/min/kg, liver resection should not be attempted. Moreover, after liver resection in patients with hepatocellular carcinoma, a higher value of ICG retention rate at 15 minutes seemed linked to a higher recurrence rate [45]. It should be noted that all these studies included patients undergoing liver resection for hepatocellular carcinoma with cirrhosis. However, Yamanaka et al. [46] reported the same result in a study of 434 patients with a subgroup of 58 patients with liver metastases. According to these results, scoring systems and decision trees have been established using ICG clearance to estimate post-operative hepatic reserve prior to liver resection. Hence, Nagashima et al. [47] proposed the chronic liver dysfunction score that included five parameters, including the ICG retention rate (with the most important weight); this score provides a reliable assessment of the risk of partial liver resection. Decision trees have also been established to select the surgical procedures in patients with impaired liver functional reserve. Imamura el al. [4], using such a decision tree, observed a mortality rate of less than 1 % in patients with Child-Turcotte-Pugh A, undergoing liver resection for hepatocellular carcinoma. In their decision tree, the possible operative procedure (enucleation, limited resection, segmentectomy, mono- to bisectoriectomy, and trisectriectomy) depended on the total bilirubin level, the presence of ascites, and the ICG retention rate at 15 minutes. ICG clearance has also been used after thoracic surgery in cirrhotic patients [48]. Iwata et al. showed, as for preoperative serum alpha-fetoprotein or total bilirubin, that the ICG retention rate at 15 minutes was a predictive factor for postoperative liver failure after lung cancer surgery in patients with liver cirrhosis. Indeed, in the liver failure group, the preoperative value of the ICG retention rate at 15 minutes was significantly higher than in the non-liver failure group [48].

Liver Transplantation

Before Liver Transplantation

Successful liver transplantation depends on numerous factors that affect either the donor or the recipient. Assessing liver function in donors remains a major problem. With this aim, Wesslau et al. [49] studied several characteristics in 41 liver graft donors, 21 of whom were accepted for transplantation. The authors observed that a

PDR-ICG value of less than 15 %/min was associated with primary non-function of the graft [49]. On the other hand, 19 livers were found unsuitable for transplantation (based on the subjective decision of the surgeon). Only three of these had a PDR-ICG value greater than 15 %/min. Thus, the ICG clearance could be used as a prognostic index prior to organ explantation.

During liver transplantation

To identify graft dysfunction, von Spiegel et al. [12] analyzed the time course of ICG elimination from before surgery until 24 h post-surgery in 9 patients (12). The authors observed that during the anhepatic phase, the Cl-ICG or PDR-ICG remained low. Immediately after reperfusion of the graft, the PDR-ICG and Cl-ICG increased to supranormal values, before decreasing during the first 24 postoperative hours. The absence, after reperfusion, of an increase in ICG elimination could, therefore, provide information on graft function. In a case report, Mandell et al. [50] suspected graft dysfunction because the ICG elimination value was similar before and after reperfusion. The intra-operative ultrasound showed a reduction in portal venous blood flow. After reconstruction, ICG elimination was normal.

After liver transplantation

The ICG elimination rate, measured either by an invasive method (Cl-ICG) or a non-invasive method (PDR-ICG or retention rate), has been widely used to evaluate graft function [14, 51–54]. These various studies showed that ICG elimination, measured on the day of liver transplantation, reflected graft function and could be used to predict graft viability and patient survival. In these studies, the authors showed a good correlation between Cl-ICG and outcome. For Jalan et al. [51] and Plevris et al. [54], a Cl-ICG cut-off of 200 ml/min predicted survival. In a recent investigation in a cohort of 72 transplant recipients, we observed that a low PDR-ICG (< 12.85 %/min) was significantly associated with postoperative complications (primary non-function, hemorrhagic or septic shock, acute rejection, hepatic artery thrombosis) (**Fig. 1**) [55]. In all the studies, the ICG elimination rate was highly sensitive of liver dysfunction but not specific for the reason of the dysfunction. Analyzing the sequential changes in our series, we showed that the PDR-ICG can be used to help identify early graft dysfunction. Indeed, among patients with a complication after liver transplantation, a persistently low PDR-ICG (< 12.85 %/min) between day 0 and day 5 was associated with septic shock, prolonged liver dysfunction or hepatic artery thrombosis (**Fig. 2**), and these patients required retransplantation or prolonged

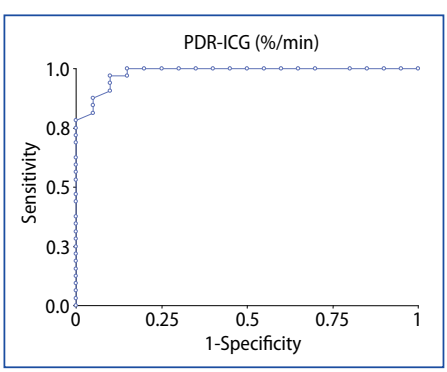

Fig. 1. Sensitivity and specificity of lowest value of plasma disappearance rate of indocyanine green (PDR-ICG) with respect to outcome according to receiver operating characteristic (ROC) curves in 72 transplant patients [55]. A PDR-ICG value, between day 0 and day 5 post-transplantation, less than 12.85 %/min is predictive of post-operative complications, with 90 % specificity and 97 % sensitivity. The area under the curve was 0.983.

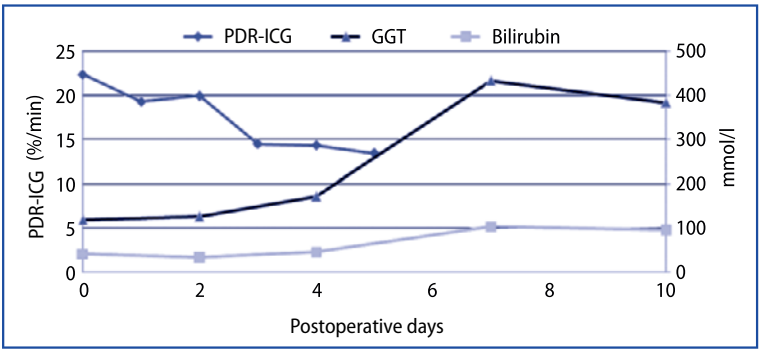

Fig. 2. Sequential changes of plasma disappearance rate of indocyanine green (PDR-ICG), bilirubin and gamma glutamyl transpeptidase, between day 0 and day 10 post-transplantation [55].

intensive medical support. Patients with a normal PDR-ICG on day 1 and day 2 after transplantation who had a secondary decrease in PDR-ICG during their ICU stay, developed acute rejection [55]. Previous studies demonstrated that acute rejection was associated with a reduction in ICG clearance due to a fall in liver blood flow [56]. We observed, only in patients with acute rejection, significant sequential changes in PDR-ICG after liver transplantation. The decrease in PDR-ICG, between the third and fifth days post-transplantation, was an early marker of acute rejection, earlier than the increase in liver enzymes.

A low PDR-ICG value after liver transplantation indicates the need for more invasive exams and should influence treatment decisions. A Doppler-ultrasound or angiography must be scheduled to look for hepatic artery thrombosis, the frequency of which ranges from 2 to 12 % after liver transplantation [57, 58]. Indeed, in our study evaluating ICG after liver transplantation, we observed four patients who had low PDR-ICG values and completely stopped blood flow in the hepatic artery [55]. In these four patients, the presence of hepatic artery thrombosis (early post-orthotopic liver transplantation), was confirmed by angiography. Moreover, treatment of the hepatic artery thrombosis (surgical repair or retransplantation) was followed by an increase in PDR-ICG. In one patient who developed hepatic artery thrombosis 13 years after orthotopic liver transplantation, the same result was obtained. Similarly, Krenn et al. [59] observed a decrease in PDR-ICG from 24.8 % (post-reperfusion) to 0 % (10 hours after admission to the ICU). Angiography showed a complete stop of blood flow in the hepatic artery, as well as in the portal vein. In this case, retransplantation was carried out as an emergency. In three other patients with normal PDR-ICG and no blood flow in the hepatic artery on Doppler-ultrasound, the diagnosis of hepatic artery thrombosis was eliminated either by angiography or computed tomography angio-scan. In these three cases, the PDR-ICG remained normal. Thus, we suggest that ICG elimination reflected by the PDR-ICG may be of considerable help in the diagnosis of hepatic artery thrombosis when the Doppler-ultrasound is difficult to interpret.

ICG clearance can be used to evaluate, as a meaningful liver function parameter, different treatments for early allograft dysfunction after liver transplantation. In primary dysfunction of the graft after liver transplantation, albumin dialysis with the molecular adsorbents recirculating system (MARS®) provides a safe approach [60, 61]. In a pilot study, evaluating the effects of MARS therapy in this situation, the

authors observed a significant increase in PDR-ICG after the treatment [60]. This PDR-ICG change before the first and the last sessions of MARS therapy was observed only among survivors. It is to be noted that, when the laboratory data on inclusion into this study were compared, only total bilirubin and PDR-ICG (4.65 %/min vs 15.8 %/min) were significantly different between the MARS treated group and the control group. Moreover, the monitoring of PDR-ICG was superior to bilirubin and prothrombin time measurements for determining graft function, especially in patients with primary non-function and graft dysfunction undergoing MARS therapy [62].

The PDR-ICG has also been used to achieve adequate blood levels of tacrolimus following liver transplantation to optimize rejection prophylaxis [63]. In this study, without finding an association between PDR-ICG and acute rejection, a mixed model analysis of variance revealed an interaction between post-operative day 1 (18 hours post-reperfusion) PDR-ICG value, and the linear increase in the blood level of tacrolimus.

Conclusion

Currently, few tests are available to evaluate liver function. Apart from static markers, such as bilirubin (the only parameter include in major prognostic scores or organ dysfunction scores), serum activities of liver enzymes or liver proteins (prothrombin time, albumin, fibrinogen), ICG clearance is the only dynamic test that can be used in clinical practice.

Over the last decade, ICG elimination, known for nearly half a century, has been used to quantify liver function and to evaluate hepatosplanchnic hemodynamics. Its prognostic value in critically ill patients and in hepatic surgery patients (hepatectomy or liver transplantation) has been demonstrated. With the use of a finger clip sensor connected to an ambulant monitor and any peripheral or central venous access (for injection of the ICG), this measure is now non-invasive, safe, and quick. A low PDR-ICG value should alert the clinician. An urgent investigation is then needed to check the patency of hepatic blood vessels and regional hemodynamics. ICG monitoring can also help guide treatment.

References

1. Poeze M, Solberg BC, Greve JW, Ramsay G (2005) Monitoring global volume-related hemodynamic or regional variables after initial resuscitation: What is a better predictor of outcome in critically ill septic patients? Crit Care Med 33: 2494–2500
2. Wheeler HO, Cranston WI, Meltzer JI (1958) Hepatic uptake and biliary excretion of indocyanine green in the dog. Proc Soc Exp Biol Med 99: 11–14
3. Ott P (1998) Hepatic elimination of indocyanine green with special reference to distribution kinetics and the influence of plasma protein binding. Pharmacol Toxicol 83 Suppl 2: 1–48
4. Imamura H, Sano K, Sugawara Y, Kokudo N, Makuuchi M (2005) Assessment of hepatic reserve for indication of hepatic resection: decision tree incorporating indocyanine green test. J Hepatobiliary Pancreat Surg 12: 16–22
5. Hunton DB, Bollman JL, Hoffman HN (1960) Studies of hepatic function with indocyanine green. Gastroenterology 39: 713–724
6. Caesar J, Shaldon S, Chiandussi L, Guevara L, Sherlock S (1961) The use of indocyanine green in the measurement of hepatic blood flow and as a test of hepatic function. Clin Sci 21: 43–57
7. Sakka SG (2007) Assessing liver function. Curr Opin Crit Care 13: 207–214
8. Sakka SG, Koeck H, Meier-Hellmann A (2004) Measurement of indocyanine green plasma disappearance rate by two different dosages. Intensive Care Med 30: 506–509

9. Purcell R, Kruger P, Jones M (2006) Indocyanine green elimination: a comparison of the LiMON and serial blood sampling methods. ANZ J Surg 76: 75 – 77
10. Hsieh CB, Chen CJ, Chen TW, et al (2004) Accuracy of indocyanine green pulse spectrophotometry clearance test for liver function prediction in transplanted patients. World J Gastroenterol 10: 2394 – 2396
11. Faybik P, Krenn CG, Baker A, et al (2004) Comparison of invasive and noninvasive measurement of plasma disappearance rate of indocyanine green in patients undergoing liver transplantation: a prospective investigator-blinded study. Liver Transpl 10: 1060 – 1064
12. von Spiegel T, Scholz M, Wietasch G, et al (2002) Perioperative monitoring of indocyanine green clearance and plasma disappearance rate in patients undergoing liver transplantation. Anaesthesist 51: 359 – 366
13. Sakka SG, Reinhart K, Meier-Hellmann A (2000) Comparison of invasive and noninvasive measurements of indocyanine green plasma disappearance rate in critically ill patients with mechanical ventilation and stable hemodynamics. Intensive Care Med 26: 1553 – 1556
14. Tsubono T, Todo S, Jabbour N, et al (1996) Indocyanine green elimination test in orthotopic liver recipients. Hepatology 24: 1165 – 1171
15. Lemmer B, Nold G (1991) Circadian changes in estimated hepatic blood flow in healthy subjects. Br J Clin Pharmacol 32: 627 – 629
16. Daneshmend TK, Jackson L, Roberts CJ (1981) Physiological and pharmacological variability in estimated hepatic blood flow in man. Br J Clin Pharmacol 11: 491 – 496
17. Svensson CK, Edwards DJ, Mauriello PM, et al (1983). Effect of food on hepatic blood flow: implications in the ”food effect” phenomenon. Clin Pharmacol Ther 34: 316 – 323
18. Geneve J, Le Dinh T, Brouard A, Bails M, Segrestaa JM, Caulin C (1990) Changes in indocyanine green kinetics after the administration of enalapril to healthy subjects. Br J Clin Pharmacol 30: 297 – 300
19. Devlin J, Ellis AE, McPeake J, et al (1997) N-acetylcysteine improves indocyanine green extraction and oxygen transport during hepatic dysfunction. Crit Care Med 25: 236 – 242
20. Sakka SG, Meier-Hellmann A (2001) Indocyanine green for the assessment of liver function in critically ill patients. In: Vincent JL (ed) Yearbook of Intensive Care and Emergency Medicine. Springer-Verlag, Heidelberg, pp 611 – 618
21. Sakka SG, Reinhart K, Meier-Hellmann A (2002) Prognostic value of indocyanine green plasma disappearance rate in critically ill patients. Chest 122: 1715 – 1720
22. Gottlieb ME, Stratton HH, Newell JC, Shah DM (1984) Indocyanine green. Its use as an early indicator of hepatic dysfunction following injury in man. Arch Surg 119: 264 – 268
23. Kholoussy AM, Pollack D, Matsumoto T (1984) Prognostic significance of indocyanine green clearance in critically ill surgical patients. Crit Care Med 12: 115 – 116
24. Pollack DS, Sufian S, Matsumoto T (1979) Indocyanine green clearance in critically ill patients. Surg Gynecol Obstet 149: 852 – 854
25. Kimura S, Yoshioka T, Shibuya M, et al (2001) Indocyanine green elimination rate detects hepatocellular dysfunction early in septic shock and correlates with survival. Crit Care Med 29: 1159 – 1163
26. Lehmann C, Taymoorian K, Wauer H, et al (2000) Effects of the stable prostacyclin analogue iloprost on the plasma disappearance rate of indocyanine green in human septic shock. Intensive Care Med 26: 1557 – 1560
27. Sander M, Spies CD, Foer A, Syn DY, Grubitzsch H, Von Heymann C (2007) Peri-operative plasma disappearance rate of indocyanine green after coronary artery bypass surgery. Cardiovasc J Afr 18: 375 – 379
28. Birnbaum J, Lehmann C, Taymoorian K, et al (2003) The effect of dopexamine and iloprost on plasma disappearance rate of indocyanine green in patients in septic shock. Anaesthesist 52: 1014 – 1019
29. Krenn CG, Krafft P, Schaefer B, et al (2000) Effects of positive end-expiratory pressure on hemodynamics and indocyanine green kinetics in patients after orthotopic liver transplantation. Crit Care Med 28: 1760 – 1765
30. Holland A, Thuemer O, Schelenz C, van Hout N, Sakka SG (2007) Positive end-expiratory pressure does not affect indocyanine green plasma disappearance rate or gastric mucosal perfusion after cardiac surgery. Eur J Anaesthesiol 24: 141 – 147
31. Henriksen JH, Winkler K (1987) Hepatic blood flow determination. A comparison of 99mTc-

diethyl-IDA and indocyanine green as hepatic blood flow indicators in man. J Hepatol 4: 66–70
32. Sakka SG (2007) Indocyanine green plasma disappearance rate as an indicator of hepatosplanchnic ischemia during abdominal compartment syndrome. Anesth Analg 104: 1003–1004
33. Hofmann D, Thuemer O, Schelenz C, van Hout N, Sakka SG (2005) Increasing cardiac output by fluid loading: effects on indocyanine green plasma disappearance rate and splanchnic microcirculation. Acta Anaesthesiol Scand 49: 1280–1286
34. Kawasaki S, Sugiyama Y, Iga T, et al (1985) Pharmacokinetic study on the hepatic uptake of indocyanine green in cirrhotic patients. Am J Gastroenterol 80: 801–806
35. Hashimoto M, Watanabe G (2000) Hepatic parenchymal cell volume and the indocyanine green tolerance test. J Surg Res 92: 222–227
36. Mukherjee S, Rogers MA, Buniak B (2006) Comparison of indocyanine green clearance with Child's-Pugh score and hepatic histology: a multivariate analysis. Hepatogastroenterology 53: 120–123
37. Herold C, Heinz R, Radespiel-Tröger M, Schneider HT, Schuppan D, Hahn EG (2001) Quantitative testing of liver function in patients with cirrhosis due to chronic hepatitis C to assess disease severity. Liver 21: 26–30
38. Merkel C, Bolognesi M, Finucci GF, et al (1989) Indocyanine green intrinsic hepatic clearance as a prognostic index of survival in patients with cirrhosis. J Hepatol 9: 16–22
39. Oellerich M, Burdelski M, Lautz HU, et al (1991) Assessment of pretransplant prognosis in patients with cirrhosis. Transplantation 51: 801–806
40. Hsia CY, Lui WY, Chau GY, King KL, Loong CC, Wu CW (2000) Perioperative safety and prognosis in hepatocellular carcinoma patients with impaired liver function. J Am Coll Surg 190: 574–579
41. Fan ST, Lai EC, Lo CM, Ng IO, Wong J (1995) Hospital mortality of major hepatectomy for hepatocellular carcinoma associated with cirrhosis. Arch Surg 130: 198–203
42. Nonami T, Nakao A, Kurokawa T, et al (1999) Blood loss and ICG clearance as best prognostic markers of posthepatectomy liver failure. Hepatogastroenterology 46: 1669–1672
43. Lau H, Man K, Fan ST, et al (1997) Evaluation of preoperative hepatic function in patients with hepatocellular carcinoma undergoing hepatectomy. Br J Surg 84: 1255–1259
44. Hemming AW, Scudamore CH, Shackleton CR, et al (1992) Indocyanine green clearance as a predictor of successful hepatic resection in cirrhotic patients. Am J Surg 163: 515–518
45. Hanazaki K, Kajikawa S, Shimozawa N, et al (2000) Survival and recurrence after hepatic resection of 386 consecutive patients with hepatocellular carcinoma. J Am Coll Surg 191: 381–388
46. Yamanaka N, Okamoto E, Oriyama T, et al (1994) A prediction scoring system to select the surgical treatment of liver cancer. Further refinement based on 10 years of use. Ann Surg 219: 342–346
47. Nagashima I, Takada T, Okinaga K, Nagawa H (2005) A scoring system for the assessment of the risk of mortality after partial hepatectomy in patients with chronic liver dysfunction. J Hepatobiliary Pancreat Surg 12: 44–8
48. Iwata T, Inoue K, Nishiyama N, et al (2007) Factors predicting early postoperative liver cirrhosis-related complications after lung cancer surgery in patients with liver cirrhosis. Interact Cardiovasc Thorac Surg 6: 720–730
49. Wesslau C, Kruger R, May G (1994) Clinical investigations using indocyanine green clearance for evaluation of liver function in organ donors. Transplantology 5: 7–9
50. Mandell MS, Wachs M, Niemann CU, Henthorn TK (2002) Elimination of indocyanine green in the perioperative evaluation of donor liver function. Anesth Analg 95: 1182–1184
51. Jalan R, Plevris JN, Jalan AR, et al (1994) A pilot study of indocyanine green clearance as an early predictor of graft function. Transplantation 58: 196–200
52. Yamanaka N, Okamoto E, Kato T, et al (1992) Usefulness of monitoring the ICG retention rate as an early indicator of allograft function in liver transplantation. Transplant Proc 24: 1614–1617
53. Hori T, Iida T, Yagi S, et al (2006) K(ICG) value, a reliable real-time estimator of graft function, accurately predicts outcomes in adult living-donor liver transplantation. Liver Transpl 12: 605–613

54. Plevris JN, Jalan R, Bzeizi KI, et al (1999) Indocyanine green clearance reflects reperfusion injury following liver transplantation and is an early predictor of graft function. J Hepatol 30: 142 – 148
55. Levesque E, Saliba F, Benhamida S, et al (2009) Plasma disappearance rate of indocyanine green: a tool to evaluate early graft outcome after liver transplantation. Liver Transpl (in press)
56. Clements D, McMaster P, Elias E (1988) Indocyanine green clearance in acute rejection after liver transplantation. Transplantation 4: 383 – 385
57. Stange BJ, Glanemann M, Nuessler NC, Settmacher U, Steinmüller T, Neuhaus P (2003) Hepatic artery thrombosis after adult liver transplantation. Liver Transpl 9: 612 – 620
58. Sánchez-Bueno F, Robles R, Acosta F, et al (2000) Hepatic artery complications in a series of 300 orthotopic liver transplants. Transplant Proc 32: 2669 – 2670
59. Krenn CG, Schafer B, Berlakovich GA, Steininger R, Steltzer H, Spiss CK (1998) Detection of graft nonfunction after liver transplantation by assessment of indocyanine green kinetics. Anesth Analg 87: 34 – 36
60. Hetz H, Faybik P, Berlakovich G, et al (2006) Molecular adsorbent recirculating system in patients with early allograft dysfunction after liver transplantation: a pilot study. Liver Transpl 12: 1357 – 1364
61. Saliba F, Ichaï P, Samuel D (2008) Artificial liver Support: Current status. In: Vincent JL (ed) Yearbook of Intensive Care and Emergency Medicine. Springer-Verlag, Heidelberg, pp 785 – 798
62. Scheingraber S, Richter S, Igna D, et al (2007) Indocyanine green elimination but not bilirubin indicates improvement of graft function during MARS therapy. Clin Transplant 21: 689 – 695
63. Parker BM, Cywinski JB, Alster JM, et al (2008) Predicting immunosuppressant dosing in the early postoperative period with noninvasive indocyanine green elimination following orthotopic liver transplantation. Liver Transpl 14: 46 – 52