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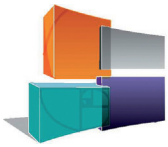

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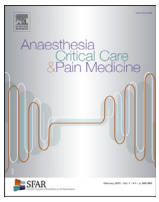

Review

Current use and perspective of indocyanine green clearance in liver diseases

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ABSTRACT

Indocyanine green (ICG) is a water-soluble anionic compound that binds to plasma proteins after intravenous administration. It is selectively taken up at the first pass by hepatocytes and excreted unchanged into the bile. With the development of ICG elimination measurement by spectrophotometry, the ICG retention test has become a safe, rapid, reproducible, inexpensive and noninvasive tool for the assessment of liver function. Clinical evidence suggests that the ICG retention test can enable the establishment of tailored management strategies by providing prognostic information. In particular, this method has been evaluated as a prognostic marker in patients with advanced cirrhosis or awaiting liver transplantation. In addition, it is used as a marker of portal hypertension in cirrhotic patients, as a prognostic factor in intensive care units and for the assessment of liver function in patients undergoing liver surgery. Since recent technology enables ICG-PDR to be measured noninvasively at the bedside, this parameter is an attractive addition to liver function and regional haemodynamic monitoring. However, the current state-of-the-art as concerns this technology remains at a low level of evidence and thorough assessment is required.

1. Introduction

During the past 20 years, major efforts have been made to develop methods for assessing hepato-splanchnic circulation and liver function parameters. As technologies have advanced, two main goals have been identified with respect to monitoring. The first is to ensure measurements using noninvasive tools so as to eliminate the risks associated with invasive monitoring. The second is to determine a single measurement that could predict overall patient status. Indocyanine green (ICG) elimination has been used as an indicator of liver function [1] since the 1950s, and the development in recent years of a noninvasive method has democratized its use.

This article briefly considers the physiology of ICG clearance and the various methods used to measure it, reviews its indications and defines the current usefulness and limitations of this monitoring method relative to hepatic functional impairment in critically ill patients with sepsis and liver disease or following major hepatic surgery, including liver transplantation.

2. Methods

A computerised search of PubMed and MEDLINE was conducted using the terms 'Indocyanine Green', 'ICG-PDR', 'ICGR15' and 'indocyanine green clearance'. The search consisted of the English language literature from 1950 to 2013. We also added personal experience and opinions.

3. Indocyanine green

The active substance in ICG dyestuff 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 daltons. ICG (ICG) is a water-soluble, non-toxic tricarbocyanine dye.

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The principal characteristic of ICG metabolism is its almost exclusive extraction by the hepatic parenchyma and almost complete elimination into the bile without entering the entero-hepatic circulation [1]. Within 1–2 seconds of its injection, ICG binds almost completely to plasma proteins (globulin, α_1-lipoproteins) without any extravascular distribution. It is captured by the parenchymal cells of the liver, bound by acceptor proteins and then excreted by the hepatic cells via the canalicular membrane, completing its elimination in the bile in an unchanged form. The elimination of ICG is therefore dependent on blood flow, cellular uptake and biliary excretion. The kinetics of ICG disappearance from the plasma have been thoroughly described in previous articles [2,3]. After its administration in patients without any perturbations, blood levels fall exponentially for about 20 minutes, by which time approximately 97% of the dye will have been excreted into the bile. Because of its metabolism, the ICG elimination rate (a dynamic test) has been widely used to assess hepatic blood flow, hepato-splanchnic haemodynamics and liver function [4–7]. Indocyanine green is generally very well tolerated and safe. No side effects were reported during any studies using ICG. However, its use is inadvisable in patients with an iodine allergy or thyreotoxicosis, because it contains iodine. In extremely rare cases, an ICG injection can cause nausea and an anaphylactic reaction (incidence of approximately 1:40,000), the principal manifestations being pruritus, urticaria, tachycardia, hypotension, dyspnoea and shortness of breath [5].

3.1. Principles of measurement

Various techniques (invasive and noninvasive) for evaluating ICG elimination after an intravenous injection are available. These methods provide clinicians with different derived values that quantify ICG elimination: its clearance (Cl-ICG) (mL/min), the plasma disappearance rate (ICG-PDR, which is the percentage of ICG eliminated in 1 minute after an ICG bolus) (%/min), and its retention rate at 15 minutes (ICGR15), which is the circulatory retention of ICG during the first 15 minutes after a bolus injection (%) (Table 1).

3.1.1. Invasive methods

Spectrophotometric concentration analysis at regular time intervals on serial blood samples was the first method described and it remains the gold standard. To reduce the number of blood samples, the cost and time spent, the insertion of a fibre-optic aortic catheter into the femoral artery has been proposed (COLD-System Z_{021}®, Pulsion Medical Systems, Munich, Germany). However, because of its invasiveness, the use of this technique is restricted to experimental settings.

Table 1
Parameters that quantify ICG elimination.

Parameter	Calculation	Normal range	Units
Plasma disappearance rate of ICG (ICG-PDR)	$\ln 2/t_{1/2} \times 100$	18–25	%/min
ICG clearance (Cl-ICG)	$Vd_{circ} \times PDR$	500–750	mL/min
ICG retention rate after 15 min (ICGR15)	$[ICG_{t=15}]/[ICG_{t=0}] \times 100$	0–10	%

ICG: indocyanine green; PDR: plasma disappearance rate; Vd_{circ}: volume of distribution of the dye.

3.1.2. Noninvasive methods

A noninvasive ICG elimination measurement by spectrophotometry was developed 15 years ago (Fig. 1). Patients are monitored using an ICG finger clip, which is connected to a liver function monitor (LiMON®, Pulsion Medical System, Munich, Germany) via an optical probe. After its injection, ICG is detected by fractional pulsatile changes in optical absorption. Optical peak absorption at 805 nm and 890 nm enables continuous measurements of PDR-ICG. For each measurement, a 0.25 to 0.5 mg/kg bolus of ICG is injected via a peripheral or central venous catheter, which is flushed immediately afterwards with 10 mL normal saline. ICG is always administered after dilution of the lyophilisate in 10 mL of solvent or ice-cold 5% dextrose, in order to obtain a concentration of 2.5 mg/mL. The dose administered is weight-related, ranging from 0.25 to 0.5 mg/kg. Sakka et al. [8] showed that in critically ill patients, an ICG assay with 0.25 mg/kg appeared to be more accurate for percutaneous measurements of PDR-ICG than a 0.5 mg/kg bolus ($r = 0.95$, $P < 0.0001$, with a mean bias of 1.0 ± 2.5%/min). The monitor then determines the PDR-ICG automatically through mono-exponential transformation of the original ICG concentration curve and backward extrapolation to the "zero"

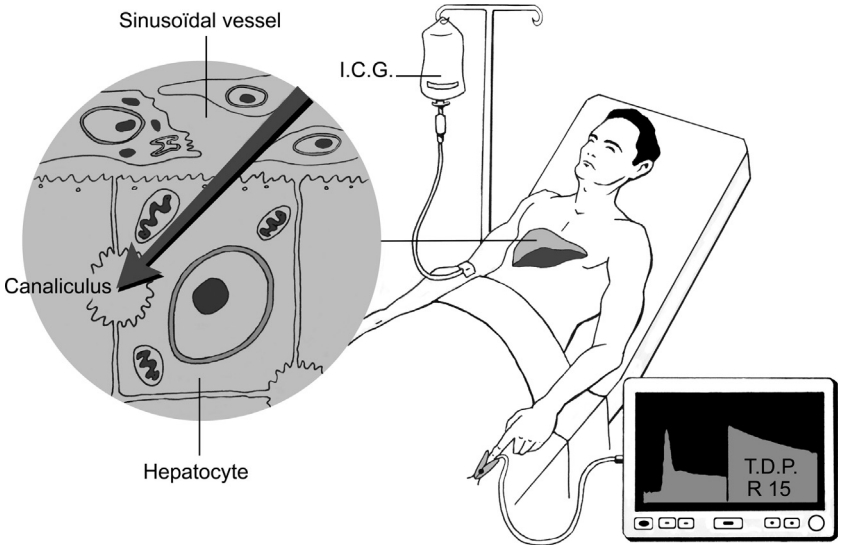

Fig. 1. Measurement principle for indocyanine green (ICG) using LiMON® (Pulsion Medical System, Munich, Germany). The patient is monitored using an ICG finger clip, which is connected to a liver function monitor via an optical probe. After injection, ICG is detected by fractional pulsatile changes in optical absorption (ICG elimination measurement by spectrophotometry). For each measurement, a 0.25 to 0.5 mg/kg bolus of ICG is injected through a peripheral or central venous catheter.

time point (100%), thus describing decay as a percentage of change per time.

Using this noninvasive monitoring technique, ICG elimination is determined without any time delay as the results are obtained within a few minutes, depending on the circulation time. It can be performed at the bedside and reduces the number of blood samples required.

Several studies have reported a good correlation between invasive and noninvasive methods (r^2: 0.81 to 0.97) [9–15] in different clinical settings, i.e. critically ill patients [13–16], patients awaiting liver transplantation, liver transplant patients [10,12,14], and those being assessed for hepatic resection [9,15].

However, ICG-PDR values should be interpreted with caution in some situations. ICG elimination is dependent on hepatic blood flow. Several factors can influence hepato-splanchnic flow, including local (such as arterial thrombosis or portal hypertension) or general factors (low cardiac output). The influence of these systemic factors on the measurement of ICG-PDR implies the need for haemodynamic stability when interpreting the values obtained. In addition, the time point at which ICG is measured is important. Indeed, circadian variations in hepatic blood flow and ICG kinetics were observed during a study in healthy male volunteers [17]. ICG elimination was at its lowest at 14:00 and its highest at night. Two previous studies demonstrated that several factors (postural change and exercise [18], food [19], drugs such as angiotensin converting enzyme inhibitors [20] or N-acetylcysteine [21]) could modify liver blood flow and thus ICG clearance. Physiologically, the ICG distribution volume has been shown to be roughly equivalent to plasma volume assessed using [^{131}I]-labelled Albumin [6]. Although renal replacement therapy changes the distribution volume, it has no influence on ICG clearance [22]. Moreover, ICG clearance values are affected by the total bilirubin concentration, because ICG and bilirubin bind to the same carrier in the transport process in hepatocytes, and therefore bilirubin is a competitive inhibitor. ICG values are 10–20% lower when the serum bilirubin level is greater than 3 mg/mL or 51 μmol/L [3]. Thus, a low measured ICG elimination should be interpreted with caution in patients with cholestasis.

3.2. Cost

ICG measurement has significant buy-in costs related to equipment purchases. The LiMON® (distributed by Pulsion Medical System, Munich Germany) monitor costs between 15,000 and 20,000 €, in France. In addition to this charge, the cost per measurement (corresponding to the cost of fluorescent dye [Infracyanine®, Serb, France]) is 45 €.

4. Clinical value of indocyanine green

Because ICG is cleared almost exclusively by the liver, this dynamic quantitative liver function test constitutes an accurate measure of specific aspects of liver function. It was initially devised to measure blood flow and subsequently employed to assess liver function by measuring functional hepatocyte mass. Today, the ICG elimination test can be used as a liver function test to evaluate patient outcomes, as a prognostic marker and as diagnostic tool in mainly two areas: in critically ill patients (in patients with or without liver failure) and in liver surgery (hepatic resection and liver transplantation) (Tables 2 and 3).

4.1. Critically ill patients without liver disease

ICG elimination was validated as a marker of hepato-splanchnic perfusion some years ago [23,24]. Studies showed that ICG clearance directly reflected total liver blood flow and was modified by acute changes in vascular liver perfusion, but only if liver function was normal. Because hepato-splanchnic hypoperfusion could lead to inadequate perfusion of the gut and damage to the intestinal mucosa, this might result in a loss of its barrier function and lead to a translocation of bacteria or endothelin into the circulation. Monitoring these factors was therefore considered essential in an intensive care setting in order to predict outcomes.

Several prognostic scores have been tested and validated in intensive care patients. In many of the latter, [Simplified Acute Physiology Score (SAPS II), Sequential Organ Failure Assessment (SOFA), etc.], total bilirubin was the only variable used to assess liver function and hepato-splanchnic blood flow. In several clinical situations in the ICU, ICG elimination has been used as a prognostic marker [23–29]. For example, during a study that included 39 critically ill surgical patients (five of whom died), ICG-PDR values were higher among survivors when compared to non-survivors (11.1 ± 7.1%/min vs. 4.8 ± 4.3%/min) [25].

All these findings were confirmed in a large retrospective cohort study, during which Sakka et al. [23] showed that ICG-PDR clearance in 336 critically ill patients admitted to the ICU was more sensitive than other scores such as the APACHE II or SAPS II, with a cut-off point $\leq$ 10.3%/min. In addition, in this series, ICG-PDR was more specific than bilirubin, the principal parameter used to detect liver dysfunction in several prognostic scores such as the SAPS II or SOFA (AUC 0.831 for ICG-PDR versus AUC 0.782 for bilirubin [$P < 0.06$], in ROC curves) [23].

Rather than using a single value, Kimura et al. showed that sequential changes in the ICG elimination rate could predict survival. In patients with septic shock, an elevation of ICG-PDR values, 24 to 120 hours after the onset of septic shock, was associated with a better outcome. By contrast, when ICG-PDR values remained stable or decreased, the patients died [30]. With the knowledge that regional variables are the most important predictors of mortality when compared with global volume-related haemodynamic parameters after stabilization [31], ICG-PDR subsequently appears to be a very useful tool in the ICU. However, in early acute inflammatory conditions, normal values of ICG-PDR should be interpreted with caution [32]. Indeed, in a porcine endotoxaemia model, the authors did not observe, despite a true hyperdynamic state, any change over time in PDR-ICG [32].

In order to evaluate the effects of treatment on hepato-splanchnic circulation, several authors have since used ICG elimination in numerous clinical situations. For example, in patients with septic shock in whom ICG elimination is predictive of survival, Lehmann et al. showed an increase in ICG-PDR after the administration of prostaglandin (PGI2 analogue – Iloprost) and a protective effect of this treatment on the hepato-splanchnic circulation [24]. The same results were observed using dopexamine [33]. ICG-PDR has also been used, in several situations, to select patients at risk for hepato-splanchnic hypoperfusion and to guide therapy or to help in choosing more invasive devices to monitor this perfusion [34–37]. In these studies, ICG elimination was used to evaluate the effects of increasing cardiac output by fluid loading on hepato-splanchnic haemodynamics.

In another setting, ICG-PDR has been used extensively to evaluate the impact of positive end-expiratory pressure (PEEP) on venous return, alterations to resulting systemic haemodynamic patterns and their effect on hepato-splanchnic blood flow. It was shown that PEEP decreased venous return and modified splanchnic haemodynamic in an experimental setting. However, following liver transplantation, and despite an increase in the PEEP (from 0 to 10 cmH_2O) and a deterioration of cardiac output in half of patients, ICG-PDR values remained normal and stable [38,39].

Table 2
Indocyanine green as a prognostic indicator in ICU.

Authors	Patients (n)	ICG values		Notes
Critically ill patients without liver disease				
Sakka et al. [23]	Critically ill patients ($n=336$)	Survivors: ICG-PDR = 16.5%/min Non-survivors: ICG-PDR = 6.4%/min	$P<0.001$	Measurement at ICU admission Better prognostic value than APACHE II (AUC = 0.68) and SAPS II (AUC = 0.75)
		AUC = 0.815 Cut-off = 10.3%/min		
Pollack et al. [26]	Trauma and septic shock patients ($n=46$)	Survivors: ICG-PDR = 15.0 ± 6.9%/min Non-survivors: ICG-PDR = 6.6 ± 5.0%/min Cut-off = 6%/min	$P<0.00051$	All patients with ICG-PDR < 6%/min died in ICU
Kholoussy et al. [25]	Surgical critically ill patients ($n=39$)	Survivors: ICG-PDR = 11.1 ± 7.1%/min Non-survivors: ICG-PDR = 4.8 ± 4.3%/min	$P<0.001$	
Kimura et al. [30]	Septic shock ($n=21$)	Survivors: K-ICG = 0.162 ± 0.035 Non-survivors: K-ICG = 0.094 ± 0.052	$P<0.0008$	K-ICG = elimination rate constant of ICG Either failure to increase the K-ICG within 20 hours or an extremely low K-ICG is a poor prognostic sign
Steinvall et al. [28]	Burn patients ($n=17$) Patients with > 20% or more of total body surface area	Cut-off: ICG-PDR < 16%/min		
Critically ill patients with liver disease				
Merle et al. [42]	Acute liver failure ($n=25$)	ICG-PDR < 6.3%/min on day 1 after ICU admission predicted a non-spontaneous outcome (death or liver transplantation) ICG-PDR < 5.3%/min at any time point predicted death or liver transplantation		7 patients underwent liver transplantation 18 patients recovered spontaneously
Feng et al. [43]	Acute liver failure ($n=61$)	ICGR15-MELD ≥ −0.4686: mortality 74.36% ICGR15-MELD < −0.4686: mortality 13.33%		The ICGR15-MELD model, Logit(P) = 0.096 × ICGR15 + 0.174 × MELD score −9.346
Stauber et al. [50]	Decompensated cirrhosis ($n=70$)	ROC curve analysis in predicting 90-day survival: for MELD: AUROC curve = 0.89; for ICG-PDR = AUROC curve = 0.71		Superior diagnostic accuracy for MELD: cut-off = 22 provided the best discrimination for prediction of 90-day survival
Merkel et al. [51]	Patients with cirrhosis ($n=105$)	Probability of survival in patients with: Cl-ICG < 300 mL/min was 35% at 48 months; Cl-ICG between 300 and 1000 mL/min was 70%; Cl-ICG > 1000 mL/min was 80%		
Lisotti et al. [45]	Cirrhotic patients ($n=96$)	ICG-PDR < 6.9%		To rule out the presence of portal hypertension

ICU: intensive care units; ICG: indocyanine green; PDR: plasma disappearance rate; MELD: model for end-stage liver disease.

4.2. Critically ill patients with liver disease

4.2.1. Acute liver failure patients

Acute liver failure (ALF) is a rapidly progressive disease with extremely high mortality. Acute assessment of disease severity is very important when making treatment decisions such as liver transplantation. Although the King's College Hospital criteria [40] are well accepted as predictive tools, their predictive accuracy is unsatisfactory [41]. The need to develop a new convenient, objective, method to predict the short-term prognosis in patients with ALF, has led some authors to analyse the clinical relevance of ICG clearance. In a prospective study, which included 25 patients

Table 3
Indocyanine green in liver surgery.

Authors	Patients	ICG value	Note
Sugimoto et al. [55]	Liver resection patients ($n=51$)	ICG-PDR < 7%/min	Predicts liver failure in the early postoperative period
Lau et al. [63]	Liver resection patients ($n=127$)	ICG-PDR > 14%/min	Safe major hepatectomy
Wesslau et al. [71]	Liver donor grafts ($n=21$)	ICG-PDR > 15%/min	Suitability for transplantation
Olmedilla et al. [83]	Liver transplant patients ($n=172$)	ICG-PDR < 10.8%/min in operating room ICG-PDR < 10%/min in operating room	Predicted severe graft dysfunction
Levesque et al. [85]	Liver transplant patients ($n=72$)	ICG-PDR < 12.85%/min	Is associated with postoperative complications
Schneider et al. [84]	Liver transplant patients ($n=86$)	ICG-PDR < 9.6%/min	Is associated with death or graft loss

ICG: indocyanine green; PDR: plasma disappearance rate.

with ALF, Merle et al. showed that measuring ICG-PDR using pulse dye-densitometry could be helpful in predicting outcome [42]. Under ROC analysis, the sensitivity and specificity of ICG-PDR values < 6.3%/min on the first day were respectively 85.7% and 88.9% in predicting a non-spontaneous recovery from acute liver failure [42]. In a series of ALF patients (n = 69), in which none were transplanted, the combination of ICGR15 and MELD scores were better than KCH criteria in predicting ALF prognosis. However, this ICGR15-MELD model (Logit[P] = 0.096 × ICGR15 + 0.174 × MELD score −9.346) and the cut-off point at −0.4684 must be validated in a large, prospective, multicentre study [43]. In addition, an analysis of sequential changes to ICGR15 values could be more relevant in the management of these patients. However, to date, data associated with a level of evidence that could support the use of indocyanine green clearance as an aid for inclusion on a liver transplantation list of patients with ALF [44] does not exist.

4.2.2. Cirrhotic patients

The prognosis and management of all chronic liver diseases is markedly dependent on whether the patient suffers from cirrhosis or not, and on the severity of the fibrotic process. It is necessary to develop accurate and reliable noninvasive methods to assess the severity of hepatic fibrosis. The ICGR15 method was recently identified as a valid tool for assessing portal hypertension and oesophageal varices in patients with compensated liver cirrhosis (Child A) with a linear correlation between ICGR15 values and the hepatic venous pressure gradient [45]. In this study, which included 96 patients, a 6.9% cut-off value was able to rule out the presence of portal hypertension (with a sensitivity of 96.6%) [45].

Moreover, the ICG elimination rate can be used to evaluate the severity of impaired liver function evaluated by different liver-specific scores. Thus, in patients with cirrhosis of various aetiologies, some authors showed that ICG-PDR values were correlated with the Child-Pugh score [46,47] or the MELD score [48,49].

In addition, as a metabolic liver function test, ICG elimination has been widely used to estimate short-term survival in decompensated cirrhosis [50,51]. However, as demonstrated by Stauber et al. [50], the MELD score was more accurate than ICG-PDR in estimating short-term survival at 90 days (AUROC curve 0.89 vs. 0.71). But it has been recently shown that in cirrhotic patients admitted to the ICU, liver-specific outcome such as the MELD score poorly predict outcome [52]. Thus, more studies are necessary to identify the role of ICG elimination, either alone or in combination with other prognostic scores (organ failure scores such as the Clif-SOFA [53]), in helping ICU specialists or hepatologists select patients who may benefit from transfer to an ICU for more aggressive treatment.

Finally, in patients with chronically impaired liver function, ICG evaluation has found a role in major surgical specialities such as hepatic surgery (described in more detail below) or liver transplantation, as well as other types of surgery. For example, Iwata et al. showed that preoperative ICGR15 values, together with serum alpha-foetoprotein and total bilirubin, could be predictive factors for postoperative liver failure following lung cancer surgery in patients with cirrhosis [54]. However, the cut-off varies according to the type of surgery.

4.3. Liver surgery

4.3.1. Hepatic resection

The incidence of liver failure after hepatectomy has decreased due to recent advances in liver surgery and perioperative care. As a fatal complication, early detection and treatment is essential. ICG-PDR values can predict liver failure in the early postoperative period [55,56]. The sensitivity and specificity of ICG-PDR values less than 7%/min on postoperative day 1 were 71.4% and 95.5%, respectively and 100% and 93.6%, respectively for predicting hospital death [55].

Many investigators have reported a relationship between preoperative ICG-PDR and postoperative outcome. Indeed, evaluation of the hepatic functional reserve is essential prior to surgery so as to limit the risks of postoperative liver failure, a life-threatening complication that occurs after 1% to 5% of hepatic resections. An accurate evaluation facilitates the choice of optimal therapy in terms of liver function: a large surgical liver resection in the case of normal liver function, or an alternative technique such as radiofrequency ablation or chemoembolization (primary treatment or temporary solution before transplantation) in the case of severe liver dysfunction [57,58].

In Asian countries, where transplantation (a viable alternative) is more problematic than in the West, ICG elimination relative to liver function has represented an important subject of research and generated a considerable number of articles. Thus, in order to predict mortality and morbidity after liver resection, several authors have used ICG clearance for the preoperative evaluation of hepatectomy for hepatocellular carcinoma (HCC), often on a cirrhotic liver, alongside imaging and volumetric assessment [59–61]. Nonami et al. [62] examined various predictive factors in 315 patients who underwent hepatic resection for HCC over an 11-year period, including 24 patients who experienced post-hepatectomy liver failure. ICG elimination and blood loss during surgery were the only independent factors correlated with survival. A 14% cut-off value for ICGR15 enabled safe major hepatectomy [63], rising to 17% in young patients and those with adequate remnant liver volume [64]. Thus, in patients with chronic liver disease requiring HCC resection, a 15% cut-off value for ICGR15 was retained [65]. Moreover, after liver resection in HCC patients, a higher ICGR15 value appeared to be linked to a higher rate of recurrence [66].

Most of the patients included in the studies discussed above underwent resections for HCC on a cirrhotic liver. The same results were observed in patients with liver metastases in the setting of abnormal parenchyma after chemotherapy [67,68].

In line with all these findings, scoring systems and decision trees were established using preoperative ICG elimination to estimate the postoperative hepatic reserve prior to liver resection [69]. Thus, Nagashima et al. [70] proposed a chronic liver dysfunction score that included five parameters, one of which the ICG retention rate (with the greatest weighting); this score provides a reliable assessment of the risks attached to partial liver resection. Decision trees were also established to select surgical procedures for patients with impaired liver functional reserve. Using such a decision tree, Imanura el al. [3] observed mortality rates lower than 1% in Child-Pugh A patients undergoing liver resection for hepatocellular carcinoma. In their decision tree, the surgical strategy adopted (enucleation, limited resection, segmentectomy or more) depended upon the total bilirubin level, the presence of ascites and the preoperative ICGR15 value.

Nevertheless, the scoring systems or decision trees are coming from mostly retrospective studies that have been performed in single centres and with small numbers of patients. Few evaluations have been made in Western countries, where most hepatic resections are performed, because of colorectal liver metastases in non-cirrhotic patients. Further investigations evaluating the accuracy of ICG-PDR in liver resection in situations such as patients with chemotherapy-induced liver damage, patients with biliary obstruction and with more information about the quality of perioperative care are expected.

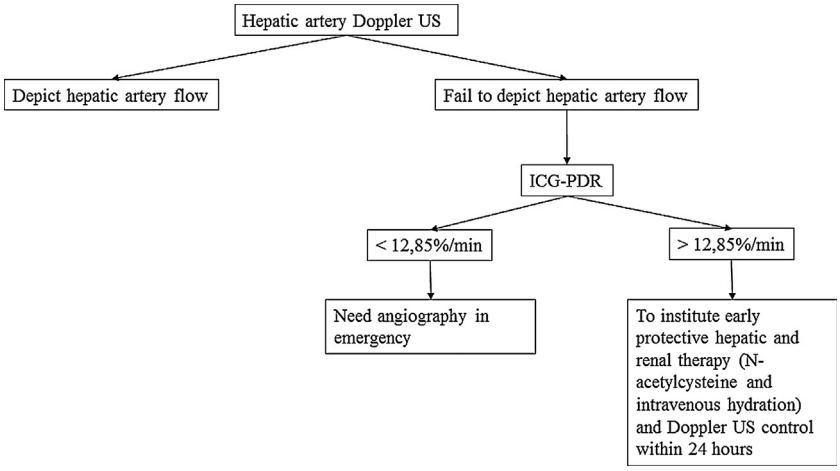

Fig. 2. Proposed decision tree for a liver transplant patient in whom a Doppler ultrasound (US) fails to depict hepatic artery blood flow.

4.3.2. Liver transplantation

ICG clearance has been largely used in the field of liver transplantation to study liver function in the donor and in the recipient.

4.3.2.1. In donor. Successful liver transplantation is dependent on numerous factors that affect either the donor or the recipient. Assessing liver function in donors remains a major problem in this period of organ shortage. In addition to the graft evaluation by the surgeon and the use of scores such as the Donor Risk Index, weak evidence suggests that the Indocyanine green elimination test might help estimate graft quality. For this purpose, Wesslau et al. [71] studied several characteristics in 41 liver graft donors, 21 of whom were accepted for transplantation. The authors found that a maximum ICG-PDR value of 15%/min was the cut-off point regarding suitability for transplantation.

4.3.2.2. In recipient: evaluation before liver transplantation. In patients with end-stage liver disease, whether patients require liver transplantation or not, and after what delay, remains an essential question. In this area, scores could optimise the timing of liver transplantation and prioritize the allocation of liver grafts. However, under our current organ allocation system, grafts are allocated to patients on the national waiting list depending on their liver disease assessed using the MELD score. But unfortunately, the survival of 15–20% of these patients cannot be predicted accurately using this score [72]. In a prospective study, Oellerich et al. [73] suggested that dynamic liver function tests such as ICG clearance were superior to conventional liver function tests in assessing the short-term prognosis of cirrhotic patients on waiting lists. Their study included 107 adult patients who were candidates for liver transplantation; 18 of them died during the 120 days following their inclusion. Those who survived for at least 120 days displayed a significantly shorter ICG half-life than the non-survivors (24.5 vs. 12.3%/min). The findings were similar among other studies [74,75]. In addition, it has been shown that the inclusion of ICG data in the MELD score contributed to an estimation of liver blood flow and rendered the new MELD-ICG score more accurate at predicting survival on waiting lists in advanced cirrhosis (MELD score of between 10 and 30) than MELD alone [76].

4.3.2.3. In recipient: morbidity risk prediction. In liver transplantation, this dynamic and quantitative liver function test has a high sensitivity for detecting any problems, i.e. for evaluating graft function and patient outcome after liver transplantation.

During the intraoperative time course, various studies have shown that ICG elimination measures well reflect graft function [12,77,78]. For example, to identify graft dysfunction, von Spiegel et al. analysed the time courses of ICG elimination from before surgery to 24 hours after surgery [12]. They observed that, immediately after graft reperfusion, these values rose to supra-normal levels, before declining during the first 24 hours after surgery. After intraoperative reperfusion, the absence of increase in ICG elimination could provide information on graft function. Indeed, Vos et al. [77] showed that a low intraoperative ICG-PDR value ($<$ 23.5%/min) predicts the occurrence of complications after liver transplantation.

Similar results have been observed in immediate postoperative situations. Several authors have shown a good correlation between ICG elimination measured in the day following LT and outcome or graft function [14,79–85]. For example, in one study that included 172 liver recipients, Olmedilla et al. [83] compared post-transplant ICG-PDR values with graft function (evaluated using a score developed by Greig et al. [86]). The authors showed that ICG-PDR measured 1 hour and then during the first 24 hours after reperfusion could accurately predict early severe graft dysfunction. ICG-PDR values were significantly lower in the group of recipients with a cut-off point of 9.6%/min that was predictive of death or graft loss [83]. Besides the diagnosis of early graft dysfunction, we showed, in a recent study, that consistently low ICG-PDR values ($<$ 12.85%/min) between postoperative day 0 (POD0) and POD5 were associated with complications [85]. We present below three particular situations where the ICG elimination rate may constitute a warning signal for clinicians:

- firstly, an analysis of sequential changes in ICG-PDR values during the first five days after liver transplantation can be used to identify acute cellular rejection [85]. Indeed, in this study which included 76 patients, we observed that acute cellular rejection was subsequently diagnosed in all patients with normal ICG-PDR values on day 1 and day 2 after transplantation, but who then experienced a secondary reduction in ICG-PDR values during their ICU stay. Previous studies had demonstrated that acute cellular rejection was associated with a reduction in ICG elimination due to a drop in liver blood flow [87]. Escorsell et al. [88] observed the same result using a cut-off point of 8.8%/min; their patients with low ICG-PDR values developed an acute rejection episode. However, this was also true for routine liver function tests (prothrombin index and total bilirubin), which enabled the diagnosis of acute rejection [88]. Nevertheless, the

fall in ICG-PDR values between the third and fifth post-transplant days constituted a marker of acute cellular rejection, which was earlier than the rise in liver enzymes [85]. Along the same idea, ICG-PDR has also been used to fine-tune adequate blood levels of immunosuppressive therapeutics (FK506) following liver transplantation in order to optimise rejection prophylaxis [89]. Although no association between ICG-PDR values and acute cellular rejection could be identified, a mixed model analysis of variance revealed an interaction between the increase of ICG-PDR elimination values and the increase in FK506 blood levels;

- secondly, ICG elimination may be a useful tool for the management of hepatic artery thrombosis (HAT), a potentially life-threatening complication following liver transplantation with an incidence of between 2% and 12% [90,91]. A Doppler ultrasound (D-US) scan or angiography should be proposed to detect this vascular complication. However, in patients with no visible hepatic artery blood flow (which is not uncommon during the postoperative period), angiography or a contrasted CT-scan are necessary to confirm the diagnosis. These investigations are not without side effects, including nephrotoxicity because of the use of contrast medium, and allergic reactions. We have observed that, in postoperative situations, a low ICG-PDR value could be associated with hepatic artery thrombosis [92]. Treatment of the latter (surgical repair or retransplantation) was followed by a rise in ICG-PDR values. Similarly, many authors observed a drop in ICG-PDR values in patients experiencing an acute total interruption of hepatic blood flow [78,93]. Clearly, in patients in whom a Doppler US fails to depict hepatic artery blood flow, a low ICG-PDR value would indicate the need for an immediate angiography in order to reconfirm and identify the degree and extension of vascular damage that will require emergency surgical repair. With a normal ICG-PDR value, an emergency angiography may not be necessary, thus providing a window of opportunity to institute early protective hepatic and renal therapy (N-acetylcysteine and intravenous hydration) (Fig. 2);
- finally, ICG elimination can be used like other meaningful liver function parameters to evaluate different treatments for early allograft dysfunction following liver transplantation. In the context of primary liver graft dysfunction, albumin dialysis with MARS® treatment constitutes a safe approach [94–96]. During a pilot study evaluating the effects of MARS® treatment in this situation, the authors observed a significant increase in ICG-PDR after treatment [93]. This change in ICG-PDR values from before to after the last session of MARS® was only observed among survivors. It was also noted that when the laboratory findings at inclusion in this study were compared, only total bilirubin and ICG-PDR (4.65%/min vs. 15.8%/min) differed significantly between the dysfunction and control arms [93].

In the context of liver transplantation, it is difficult to interpret a single ICG-PDR measurement. But associated with biological or clinical parameters, and also the performance of several successive measurements, these values constitute a valuable aid for clinicians in the management of transplant patients during the postoperative period. Low ICG-PDR values should alert clinicians and trigger urgent investigations to check the patency of hepatic blood vessels and regional haemodynamics, and thus guide treatment. However, the exact role of ICG (time of measure, tree decision, scoring system including ICG-PDR) requires further evaluation because the results are from small studies that have not yet been confirmed by larger prospective studies.

5. Conclusion

ICG elimination is a global function parameter that is dependent on liver perfusion, sinusoidal uptake, adenosine triphosphate-dependent excretion into biliary canaliculi and unrestricted biliary drainage, which should be considered and interpreted in an individual clinical context. Liver function quality and hepatic blood flow can be evaluated from the clearance of this non-toxic compound.

However, the use of the test is carried out in only a few research centres and in clinical practice in few indications (such as the assessment of the liver function before resection). Since more recent technology enables noninvasive ICG-PDR measurement at the bedside, this parameter seems to be an attractive addition to liver function and regional haemodynamic diagnostic tools. In addition, the data suggest that assessing disease severity and outcome at a single time point is potentially fraught with difficulty. Instead, a "multistep" approach for complex patients that evolves with time and seeks to identify treatment "responders", might be advocated.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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