Anaesthesia 2014, 69, 1364–1376 doi:10.1111/anae.12755

Review Article

Green light for liver function monitoring using indocyanine green? An overview of current clinical applications

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Summary

The dye indocyanine green is familiar to anaesthetists, and has been studied for more than half a century for cardiovascular and hepatic function monitoring. It is still, however, not yet in routine clinical use in anaesthesia and critical care, at least in Europe. This review is intended to provide a critical analysis of the available evidence concerning the indications for clinical measurement of indocyanine green elimination as a diagnostic and prognostic tool in two areas: its role in peri-operative liver function monitoring during major hepatic resection and liver transplantation; and its role in critically ill patients on the intensive care unit, where it is used for prediction of mortality, and for assessment of the severity of acute liver failure or that of intra-abdominal hypertension. Although numerous studies have demonstrated that indocyanine green elimination measurements in these patient populations can provide diagnostic or prognostic information to the clinician, 'hard' evidence – i.e. high-quality prospective randomised controlled trials – is lacking, and therefore it is not yet time to give a green light for use of indocyanine green in routine clinical practice.

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Accepted: 27 April 2014

Introduction

Although most anaesthetists are probably aware of the existence of the dye indocyanine green (ICG), fewer will have direct experience of its use in anaesthesia and surgery. As it may well be increasingly used in the future, a summary of its pharmacology and a literature review is apposite to highlight potential clinical indications for the use of ICG clearance.

Indocyanine green is a non-toxic, inert, anionic water-soluble tricarbocyanine dye, with an ideal absorption maximum at an isobestic point of haemoglobin, making spectrophotometric determination of ICG independent of oxygen saturation and serum bilirubin concentration (Fig. 1).

After intravenous injection, ICG is bound mainly to α1-lipoproteins and its distribution volume approximates the plasma volume [1]. Indocyanine green is almost exclusively extracted by the liver through selective uptake by the organic anion transporting polypeptide 1B3 and by Na^+-taurocholate co-transporting polypeptide [2]. Uptake is followed by biliary excretion without metabolism and enterohepatic re-circulation, and thus elimination is considered to correlate with hepatic function.

In-vivo ICG detection reveals a typical indicator-dilution curve after intravenous bolus administration with an initial peak, a second re-circulation peak and an elimination phase [3]. The primary peak (A, Fig. 2),

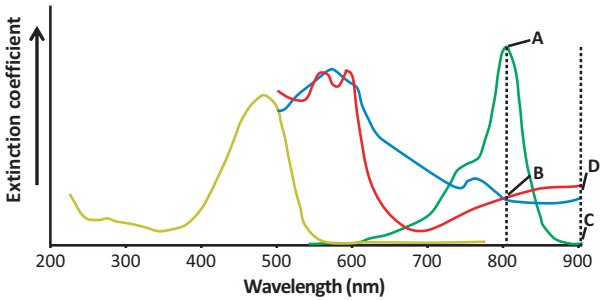

Figure 1 Absorption spectra of indocyanine green (ICG; green line), bilirubin (yellow line) and haemoglobin (red line for oxyhaemoglobin and blue line for reduced haemoglobin). Pulse dye densitometry measures relative ICG concentration at 805 nm (ICG peak absorption, A) and at 905 nm (no ICG absorption, C). Points B and D show the independancy of this measurement from arterial oxygen saturation.

which can be used for cardiac output calculation [4], is followed by the re-circulation phase (B, Fig. 2), and is sometimes followed by smaller peaks. This phase represents ICG distribution in the body, and allows determination of circulating blood volume [5–7]. The third phase is the hepatic elimination phase (C, Fig. 2) and lasts 10–20 min [8]. The curve exhibits bi-exponential decay with linear kinetics up to injected doses of 1.0 $mg.kg^{-1}$ [8]. Indocyanine green has an approximate half-life of 3–4 min, but this can be substantially prolonged in patients with liver disease.

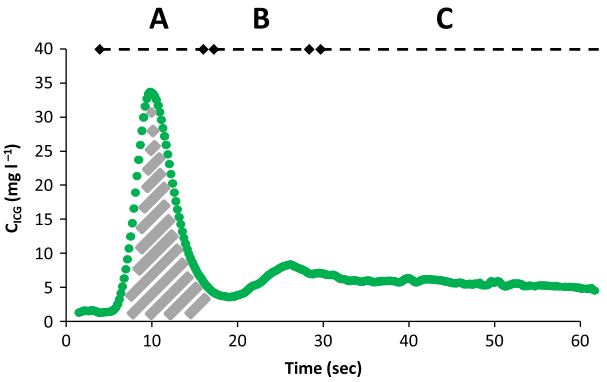

Figure 2 Example of a typical ICG indicator-dilution curve. ICG, indocyanine green; C_{ICG}, ICG blood concentration. A: primary peak, B: secondary peak (re-circulation phase), C: (hepatic) elimination phase. The shaded grey area represents the area under the primary curve, allowing cardiac output calculations. The remainder of the elimination phase is not shown in this figure, but PDR_{ICG} can be calculated in this phase by curve fitting using dynamic backward extrapolation (see text and Table 1).

Intravenous use of ICG is associated with a low incidence of mostly transient and mild allergic reactions (e.g. urticaria, headache) [9], whereas moderate or severe reactions are rare, and most probably associated with non-immunological histamine release [9–11]. Administration of ICG may be contraindicated in patients with known iodine allergy or thyrotoxicosis (5% of the molecule is coated with iodine), although there is no existing literature on this issue.

The aforementioned properties of ICG provide the anaesthetist with a bedside assessment of cardiovascular function, and hepatic function and blood flow – indications for which it has been in use for many decades [7, 12, 13]. The dye is also increasingly used for other indications by other allied specialties, e.g. by surgeons for identifying tissue and vessels during neurovascular and oncologic surgery, and in the assessment of microvascular circulation [14, 15]. The use of ICG for these non-anaesthetic indications is beyond the scope of this review.

Methods

We performed a MEDLINE-based search of literature published up to November 2013 using the following key-words: indocyanine green; ICG; indicator-dilution technique; liver function; liver transplantation; hepatic resection; (acute) liver failure; and mortality prediction. Articles we identified were also manually scanned for further relevant references. We only considered human studies published in English or German.

To assess the methodological quality of the articles, the JADAD score was calculated for each article [16]. This 5-point scoring system summarises the level of evidence by giving points for study design characteristics, such as the adequacy of randomisation, blinding and description of dropouts. None of the identified studies achieved a JADAD score > 0, as they were either retrospective or were non-randomised prospective (observational) studies.

Liver function monitoring using ICG

As a static liver function test, ICG can be used for measurement of hepatic blood flow using the Kety–Schmidt technique, an adaptation of the Fick principle

Table 1 Frequently used variables for quantification of hepatic indocyanine green (ICG) extraction.

Variable	Description	Unit	Calculation	Normal value
PDR_{ICG}	ICG plasma disappearance rate	% min^{-1}	Backward extrapolation of k, curve fitted as: $C_{ICG}(t) = C_0 * e^{-k \times t}$	> 18
Cl_{ICG}	ICG clearance	$ml.min^{-1}.kg^{-1}$	$k * V_D$	6–12
ICGR15	ICG retention ratio after 15 min	%	$(C_{ICG\ (15)}/C_{ICG\ (0)}) * 100$	< 10
$ICG_{t\ 1/2}$	ICG half-life	min	$(\ln 2 * V_D)/Cl_{ICG}$	3–5

e = Euler's number (approximately 2.718); k = fractional ICG concentration change per minute; t = time (min); V_D = ICG volume of distribution; $C_{ICG\ (t)}$ = ICG concentration at time point t (min); Cl_{ICG} = ICG clearance ($ml.min^{-1}.kg^{-1}$).

[17]. In short, hepatic blood flow can be calculated from the difference in hepatic artery and vein ICG concentration, measured once a stable plasma ICG concentration has been reached during continuous ICG infusion. Although accurate, this technique is not feasible in a clinical setting as it is invasive, requires multiple arterial and venous blood samples, and only provides an assessment of hepatic blood flow and not of function. Instead, it is more common to use ICG in the context of a dynamic liver function test.

All dynamic, quantitative liver function tests are based on the assumption that the hepatic clearance of a compound is the product of the compound-specific extraction rate and the effective hepatic blood flow [18]. In the case of ICG, hepatic clearance of ICG is highly dependent on hepatic blood flow because the ICG hepatic extraction rate is very high. Therefore, dynamic liver function monitoring with ICG is regarded as a surrogate of both intrinsic liver function and hepatic blood flow, and so can only adequately assess liver function if measured under steady-state haemodynamic circumstances [13, 19, 20].

The gold standard for quantifying hepatic ICG clearance is ex-vivo photometric analysis of consecutive arterial blood samples, obtained in a time frame up to 15 min after intravenous bolus injection [13, 21]. Subsequently, a concentration–time curve can be drawn from which the absolute clearance of ICG or the fractional change per minute can be calculated. Although this technique is accurate and reproducible, it is invasive, complex and time consuming.

Nowadays, the elimination of ICG can be accurately assessed in vivo via an intravascular fibreoptic sensor (invasive), or by transcutaneous non-invasive pulse dye densitometry (PDD), an easily applicable bedside technique with a sensor placed on a finger or the nose [22–24]. In patients with both stable and unstable haemodynamics, ICG elimination measurements by PDD correlate adequately (R^2 = 0.77–0.97) with invasively determined fibreoptic values [25–28], although they might underestimate the true value, as was demonstrated in 70 patients with liver cirrhosis [29]. Pulse dye densitometry measures ICG concentration by determining the relative changes in light absorption by ICG in arterial blood at two wavelengths: at 805 nm (peak absorption frequency of ICG; point A in Fig. 1); and at 905 nm (frequency at which ICG exhibits no absorption; point C in Fig. 1) [25]. As absorption by oxyhaemoglobin and reduced haemoglobin is similarly low at both wavelengths (see B and D in Fig. 1), haemoglobin oxygen saturation has no influence on measured ICG values. Likewise, the concentration of bilirubin (peak absorption 470 nm) has no effect on measured ICG blood concentrations.

Two commercially available systems are capable of transcutaneous PDD ICG concentration measurements: the LiMON device (Pulsion Medical Systems, Munich, Germany); and the DDG2001 analyser (Nihon-Khoden, Tokyo, Japan). Both devices calculate the rate constant (k) of the ICG indicator-dilution curve using backward dynamic extrapolation (Table 1) of the elimination phase (phase starting at point C, Fig. 2). The k-value is then multiplied by 100 to obtain the plasma disappearance rate of ICG (PDR_{ICG}) in percentage per minute. The PDR_{ICG} and the ICG retention ratio after 15 min (ICGR15) are the most widely used variables for quantification of hepatic function (Table 1).

It should be stressed that in-vivo measurement of ICG allows detection of *relative* changes in ICG concentrations, and thus determination of ICG elimination rate only. Ex-vivo measurement of ICG allows *absolute* ICG concentration determinations and thus calculation

of its distribution volume as well as ICG clearance in $ml.min^{-1}.kg^{-1}$ (Table 1). There is good correlation between PDR_{ICG} and $ICG_{clearance}$ and they show similar trends when measured repeatedly [20, 27].

In 1964, the normal value of ICG plasma disappearance rate was estimated in healthy subjects to be 23.5% min^{-1} (mean) with a range from 18.7 to 30.1% min^{-1} [21]. This early finding is still supported by more current literature, as a $PDR_{ICG} < 18\%\ min^{-1}$ is regarded as being indicative of hepatic insufficiency [30, 31]. In a recent study, a relatively wide range of PDR_{ICG} values (9.7–43.2% min^{-1}, mean 23.2% min^{-1}) was found in patients undergoing elective non-hepatic surgery [24]. These measurements were derived during induction of anaesthesia, and probably reflected the variable systemic and hepatic haemodynamic consequences of anaesthetic induction [32].

In general, elimination of ICG is influenced by either hepatic blood flow or the intrinsic ability of the liver to eliminate ICG. Factors that influence hepatic blood flow can be further subdivided into local and systemic factors. A localised decrease in hepatosplanchnic blood flow, for example due to hepatic artery thrombosis or intra-abdominal hypertension, decreases the elimination of ICG [33, 34]. Systemic haemodynamics that influence hepatosplanchnic perfusion (e.g. a low cardiac output) can also decrease ICG elimination [19, 35]. General anaesthetic agents do not influence the elimination of ICG directly, but can reduce elimination indirectly by affecting haemodynamics (see below) [36–38]. In contrast, local or systemic factors that increase hepatosplanchnic perfusion can cause an increased PDR_{ICG} value because of the high hepatic ICG extraction ratio [20]. Liver function can thus only be measured reliably under 'steady state' haemodynamic conditions, because of the dependency of ICG clearance on hepatic blood flow [13, 19, 20]. Other factors, including serum bilirubin, serum albumin, body weight and age, can also influence ICG clearance [39].

A decrease in the intrinsic ability of the liver to extract ICG from the circulation can reduce ICG elimination. This can be caused by global hepatocellular dysfunction, for example in end-stage liver disease or during graft rejection after liver transplantation, but might also be caused by cholestasis. The latter might be caused by a reduced uptake of ICG, as bile salts may inhibit Na^+-taurocholate co-transporting polypeptide mediated ICG uptake, whereas bilirubin might competitively inhibit ICG uptake by the organic anion transporting polypeptide 1B3. The exact interaction between ICG and bilirubin transport carriers has yet to be elucidated [2, 40]. As a result, a low measured ICG elimination should be interpreted with caution in patients with obstructive jaundice [41, 42].

The factors known to decrease ICG elimination should be borne in mind when interpreting the results of ICG clearance tests, and are summarised in Fig. 3. In addition, 'normal' values of ICG elimination can show variation between specific patient populations (e.g. those post-liver transplantation vs those in septic shock), and therefore there is no single normal value applicable to all patient groups. Clinicians should be aware of this when assessing liver function using ICG clearance (see Table 2 for cut-off values applying for specific indications). While a single ICG elimination measurement might be sufficient for some indications (e.g. pre-operative screening of liver transplant recipients), for other indications (e.g. function assessment after liver transplantation) a series of ICG elimination measurements is preferable. The accuracy of ICG elimination measurements may be decreased by technical artefacts caused by patient motion, or by inadequate pulse contour tracing in the case of reduced peripheral perfusion, particularly in the critical care setting. Repeated ICG administration within 30 min may result in a baseline drift (caused by remnant ICG), incorrectly suggesting an increased PDR_{ICG}.

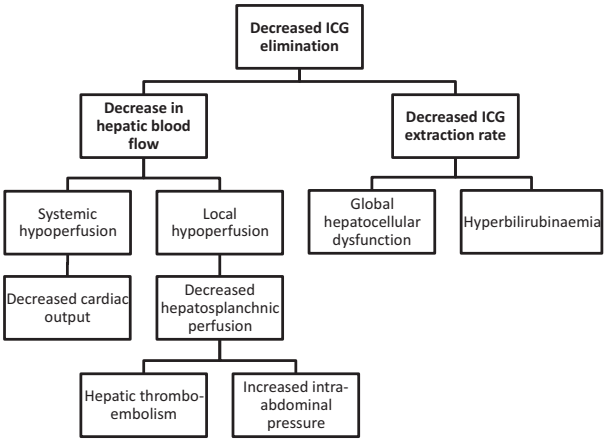

Figure 3 Factors contributing to a decreased elimination of indocyanine green (ICG).

Table 2 Indications for use of indocyanine green (ICG) elimination measurements with associated cut-off values as found in the literature.

Indication	Phase or specific setting	Cut-off value
Major hepatic resection	Pre-operative	ICGR15 $\leq$ 14% safe to perform major hepatic resection ICGR15 15–20 only safe if estimated remnant volume is sufficient
	Postoperative	PDR_{ICG} < 7% min^{-1} indicative for development of postoperative hepatic failure
Paediatric liver transplantation	Insufficient data available in the literature	
Adult liver transplantation	Pre-operative	PDR_{ICG} 22% min^{-1} best cut-off for 90-day mortality Specifically useful for incorporation of PDR_{ICG} in the MELD score range between 10 and 30
	Intra-operative	PDR_{ICG} 10.8% min^{-1} 60 min after graft reperfusion best cut-off for serious graft dysfunction
	Postoperative	PDR_{ICG} 10–13% min^{-1} as cut-off for early serious graft dysfunction Decreasing trend in PDR_{ICG} might suggest acute graft rejection
Critically ill patients	Overall mortality prediction	Multiple PDR_{ICG} cut-off values found: Overall: 6.4% min^{-1} vs 16.5% min^{-1}, non-survivors vs survivors Septic shock: 12.1% min^{-1} vs 21.2% min^{-1}, non-survivors vs survivors
	Acute liver failure	> 6.3% min^{-1} predictive of spontaneous recovery (adults) < 5.9% min^{-1} predictive of transplantation requirement (paediatrics)
	Intra-abdominal hypertension	PDR_{ICG} < 18% min^{-1} indicative of intra-abdominal hypertension

ICGR15, retention ratio 15 min after ICG administration; PDR_{ICG}, indocyanine green plasma disappearance rate; MELD, Model For End-Stage Liver Disease.

Peri-operative point-of-care monitoring using ICG kinetics after hepatectomy

There is ongoing debate about the peri-operative value of ICG as a dynamic liver function test. Numerous studies have demonstrated the role of ICG as a pre-operative planning tool, whereas in the intra- and postoperative phase, ICG may serve a role as a point-of-care liver function monitoring tool.

Indocyanine green may have a role in assessing the maximum extent of major hepatic resection that will not cause postoperative liver failure. This serious complication occurs in 5–8% of patients, and is associated with a high mortality rate [43, 44]. Although the liver has a unique ability to regenerate by hyperplasia, even after extended surgical resection, its ability to regenerate can be diminished in patients with pre-existing liver disease (particularly those with liver cirrhosis), resulting in an increased risk of postoperative hepatic failure. Generally, assessments of resectability are based on clinical judgment (presence of jaundice and/or ascites), results of routine biochemical tests (e.g. bilirubin, aspartate/alanine aminotransferase and alkaline phosphatase), and prediction of liver remnant volume using CT or MRI imaging. Further investigations are usually unnecessary in the absence of clinical and biochemical signs of liver dysfunction [45]. For those patients with pre-operative signs of liver dysfunction, multiple scoring systems can be used for assessing whether major hepatic resection is possible. The most commonly used scoring systems are the Child–Pugh score and the Model for End-Stage Liver Disease (MELD) score. There is uniform agreement that patients with a Child–Pugh C classification or a MELD score > 14 are unsuitable for any hepatic resections, whereas patients with Child–Pugh classification B or a MELD score between 9 and 14 should be thoroughly evaluated to determine whether, and to what extent, a minimal resection is possible [43, 45, 46].

In two retrospective studies in patients with liver cirrhosis, impaired pre-operative ICG elimination was independently associated with postoperative mortality

and hepatic failure, whereas conventional liver function tests (e.g. bilirubin, albumin) were not [47, 48].

Incorporation of the ICGR15 measurement (ICG retention ratio after 15 min) in pre-operative work-up protocols has resulted in near-zero mortality rates, demonstrating its potential usefulness in risk assessment of cirrhotic patients requiring major hepatic resection [40, 49, 50]. In these large single-centre retrospective analyses, ICGR15 was measured pre-operatively to assess the possible extent of hepatic resection in patients with Child–Pugh A status without either ascites or hyperbilirubinemia. An ICGR15 < 15% is generally used as cut-off value for suitability for major hepatic resection [51–54], although in one protocol, (extended) right hepatectomy was allowed with a ICGR15 > 10%, and a left hepatectomy if ICGR15 was 10–20% [50–52]. If the estimated remnant liver volume is sufficient, then patients with a slightly higher ICGR15 (15–20%) can successfully undergo major hepatic resection [40, 55, 56]. When ICGR15 is 15–20% and the estimated remnant liver volume is insufficient, pre-operative portal vein embolisation can be performed to increase remnant liver volume by inducing hyperplasia of liver lobules perfused by the contralateral portal vein. The ICGR15 values correlate with volumetric changes of the liver following portal vein embolisation [57]. The clinical applicability of ICG elimination assessment after portal vein embolisation is unknown, but the test might still reflect liver function properly due to a combination of preserved overall hepatic blood flow and hepatocyte hyperplasia [58].

Assessment of ICGR15 may have a prognostic role in patients with other pathologies. One retrospective study in patients with hepatolithiasis (n = 144) showed a significantly lower incidence of postoperative liver failure when patients were selected using the ICGR15 test instead of the Child–Pugh scoring system [59].

All studies to date have been performed in single centres, and thus results may be dependent on factors that vary by institution, such as the specific surgical techniques and associated variations in blood loss, and the overall quality of peri-operative care [55]. Large randomised multicentre studies are required to account for these factors and develop uniform standards for pre-operative assessment of patients requiring major hepatic resection. In addition, most studies were undertaken in Asian countries, where resection for hepatocellular carcinoma in a cirrhotic liver is common. This is in contrast to Western countries, where most hepatic resections are performed because of colorectal liver metastases in non-cirrhotic patients. Nevertheless, these patients have frequently received neo-adjuvant chemotherapy, which can lead to chemotherapy-induced liver parenchymal damage. This, in combination with (chemotherapy-associated) steatohepatitis, might compromise liver function and regenerative ability when major hepatic resection is intended. Assessment of ICG elimination may be of particular use in the pre-operative work-up of this population, as the MELD score fails to predict outcome after major hepatic resection in non-cirrhotic patients [60]. Recent evidence shows conflicting results regarding the accuracy of ICG elimination in reflecting chemotherapy-induced liver damage, reflecting the importance of further investigation of the technique [61–63].

Finally, in patients with biliary obstruction, a decreased ICGR15 value may be found, possibly falsely suggesting impaired liver function [41, 42]. In these patients, the pre-operative ICGR15 value should be interpreted with caution, and should not be used to justify withholding intended curative surgery.

During major (extended) hepatectomy, information on the maximum extent of liver resection unlikely to cause postoperative hepatic failure may be desirable. In a single-centre study (n = 29) of patients undergoing major hepatectomy, peak postoperative serum bilirubin concentrations correlated closely with ICGR15 measured both before clamping (R = 0.64) and during parenchymal transection (R = 0.72) [64]. Intra-operative PDR_{ICG} and ICGR15 values also correlated with serum lactate during hepatic inflow occlusion and hospital length of stay, respectively [65]. Furthermore, an intra-operative $PDR_{ICG} < 9\%\ min^{-1}$ was found to predict postoperative hepatic failure with a sensitivity of 88% and a specificity of 82% [53]. Although these measurements were performed after completion of parenchymal transection, they correlated closely (R = 0.8) with values obtained after hepatic inflow occlusion, before the start of parenchymal transection.

In the early postoperative phase following major hepatic resection, low PDR_{ICG} values are associated with the development of hepatic failure [66–68]. In

one study, a PDR_{ICG} value < 7% min^{-1} measured on the first postoperative day was associated with development of hepatic failure 2–5 days later.

Peri-operative point-of-care monitoring using ICG kinetics in liver transplantation

The role of ICG in liver transplantation has been studied in both donors and recipients. The following section will discuss the potential benefit of using ICG for assessing graft suitability in donors, as an additional screening tool in the pre-operative phase and as a point-of-care liver function monitoring tool in the intra- and postoperative phase in recipients.

A major problem within the field of liver transplantation is the shortage of donor organs [69]. To widen the pool of potential donors, donation after circulatory death and the use of marginal or extended criteria donor livers (i.e. grafts from older donors, after a prolonged ICU stay, or with a higher degree of liver steatosis) are being accepted in a growing number of countries [69–71]. The donor risk index, based on multiple donor characteristics such as age, height and cause of death, is predictive of long-term graft failure [72]. In this context, weak evidence suggests that measurement of PDR_{ICG} in potential donors might assist in the assessment of graft suitability. One retrospective single-centre study showed that a PDR_{ICG} value < 15% min^{-1} measured in donor patients before organ retrieval was predictive of a subjective intra-operative surgical decision to transplant or reject the graft [73]. Of note in this study, both transplanted organs in which PDR_{ICG} had been < 15% min^{-1} later showed primary non-function. In another study, the donor ICG clearance was weakly inversely correlated with recipient postoperative peak prothrombin time (PT) and serum bilirubin (R = −0.32 and −0.38, respectively) [74]. These small studies have not yet been followed by larger prospective studies.

The MELD score is the most widely used scoring system for prioritisation of patients awaiting transplantation and replaced the Child–Pugh score [75]. Indocyanine green elimination kinetics in both paediatric and adult patients awaiting liver transplantation are more accurate in predicting short-term mortality than either the Child–Pugh score or conventional laboratory measurements (i.e. serum bilirubin, PT, albumin) [76]. Comparisons of the MELD score with the PDR_{ICG} value for the prediction of short-term survival in patients on the waiting list for liver transplantation are conflicting [77, 78]. It has, however, been shown that combining ICG elimination with the MELD score (MELD-ICG score) may further improve the accuracy of survival prediction compared with the use of the MELD score alone, which was not true for other dynamic liver function tests (MEGX and GEC tests) [79]. The significantly improved accuracy of the ICG-MELD score was found for patients with an intermediate/advanced original MELD score of between 10 and 30 points, showing that ICG elimination measurement might have an additional prognostic role in this specific patient group.

The intra-operative time course of PDR_{ICG} during liver transplantation has a typical pattern [20]. Following induction of anaesthesia, the ICG elimination rate is relatively low due to haemodynamic compromise. During the anhepatic phase it decreases to almost zero. After graft reperfusion, elimination of ICG is restored to supra-normal values, reflecting adequate hepatic perfusion and immediate liver function [20]. Accordingly, a decreased PDR_{ICG} after reperfusion might be indicative of immediate graft dysfunction. In one analysis of 172 consecutive patients undergoing liver transplantation from deceased donors, serious graft dysfunction developed in 10 patients (defined as a combination of serum AST > 2500 $U.L^{-1}$, absence of bile production and development of severe coagulopathy within 72 h after transplantation) [80]. A PDR_{ICG} < 10.8% min^{-1} measured 60 min after reperfusion of the liver graft predicted serious graft dysfunction, whereas a PDR_{ICG} > 10.8% min^{-1} had a 99.2% negative predictive value. Comparable results were found for values measured on the first postoperative day. Another study (n = 62) suggested that a PDR_{ICG} value > 23.5% min^{-1} measured at the end of surgery could predict absence of early postoperative complications following liver transplantation [81]. Other case series provide confirmative evidence of the prognostic value of intra-operative PDR_{ICG} measurements with regard to critical intra-operative reduction in portal vein flow [34] and primary graft non-function [20]. In one case, thrombosis of the portal vein was not associated with a decreased elimination of ICG, probably owing to unstable haemodynamics [82]. In addition to portal hypoperfusion,

*hyper*perfusion of the portal vein in the context of living donor liver transplantation is associated with reduced graft survival due to the risk of developing functional 'small-for-size' graft failure. Recent reports have suggested that PDR_{ICG} values might be a valuable monitoring tool in surgical interventions aimed at modulating portal venous pressure [83, 84].

Liver function monitoring with clinical observation or conventional laboratory tests requires time, and is unable to detect acute changes in early postoperative liver function. Moreover, it is difficult to assess early graft function accurately based on one diagnostic method alone [85, 86]. Therefore, several scoring systems have been developed based on a combination of conventional laboratory measurements and clinical examination (examples include the Ploeg and the Gonzalez criteria) [87–89]. Unfortunately, the correlation between these criteria is very poor when they are used to diagnose severe graft dysfunction [86], and thus better diagnostic techniques are needed in the early phase following liver transplantation. A pilot study using postoperative measurement of ICG clearance (invasively determined) to monitor graft function showed that preserved ICG clearance strongly predicted normalisation of acidosis and PT, whereas invasively measured ICG clearance < 200 ml.min^{-1} predicted early death or the need for re-transplantation [90]. Further studies have shown that in the early postoperative phase after orthotopic liver transplantation, a non-invasively determined PDR_{ICG} value below 10–13% min^{-1} was predictive of subsequent serious early graft dysfunction [80, 91, 92]. In addition, a decrease in PDR_{ICG} values from 25.5 $\pm$ 4.8% min^{-1} at the first postoperative day to 10.3 $\pm$ 2.5% min^{-1} at the fifth postoperative day predicted acute graft rejection, suggesting that absolute PDR_{ICG} values as well as its time course are important [92]. Low postoperative PDR_{ICG} values may be associated with the development of hepatic artery thrombosis [93]. In contrast, however, one study in which PDR_{ICG} was measured 24–72 h after transplantation failed to demonstrate a difference in PDR_{ICG} values between patients with and without complications [94].

In recipients of a living donor graft, a PDR_{ICG} cut-off value of 18.0% min^{-1} 24 h after transplantation was able to predict prolonged jaundice (> 2 weeks), and these PDR_{ICG} values were also closely correlated with graft parenchymal damage scores based on standardised histopathological examination [31].

The Maximal Enzymatic Liver Function (LiMAx) test has recently been investigated in a pilot study (n = 99) [95]. With this test, ^{13}C-methacetin, which is metabolised by hepatic cytochrome P450 enzymes to paracetamol and $^{13}CO_2$, is administered intravenously. Continuous and non-invasive breath analysis of $^{13}CO_2$ production is measured as a surrogate of maximal liver metabolic capacity. This test seemed to have a better ability to predict primary non-function and initial dysfunction (defined as surgical re-intervention or re-transplantation within 2 and 14 days, respectively) than PDR_{ICG} measurements and conventional laboratory measurements such as serum AST/ALT and serum bilirubin [95]. Interestingly, PDR_{ICG} values in the control group were relatively low (15.5 $\pm$ 6.4% min^{-1} vs 11.8 $\pm$ 6.1% min^{-1}, respectively), and did not agree with values found in previous studies [31]. The exact role of the LiMAx test, which is time-consuming, expensive and difficult to perform, requires further evaluation.

Use of ICG in the critically ill

In critically ill patients, ICG measurements may assist with disease severity assessments and accurate mortality risk prediction, which may help to inform therapeutic strategy decisions.

Scoring systems based on clinical and biochemical variables are frequently used for mortality risk prediction and for grading the severity of critical illness [96]. A large retrospective study (n = 336) has shown that the ability of PDR_{ICG} measurement to predict mortality in ICU patients is similar to that of the more complex but frequently used APACHE II and SAPS II scores [97]. Of note, low PDR_{ICG} correlated with mortality (PDR_{ICG} was 6.4% min^{-1} vs 16.5% min^{-1} in non-survivors and survivors, respectively), irrespective of the underlying disease, concordant with previous studies [98, 99]. Among patients admitted to the ICU after undergoing coronary artery bypass surgery, low PDR_{ICG} values independently predicted prolonged ICU stay [100]. In addition, another study in post-cardiac surgery patients (n = 190) found that both pre- and postoperatively measured ICGR15 values could aid in the prediction of prolonged ICU stay [101].

In a small study in septic ICU patients, non-survivors (n = 18) showed a significantly lower PDR_{ICG} value compared with survivors (n = 22) (12.1% min^{-1} vs 21.2% min^{-1}, respectively), and 89% of patients with a PDR_{ICG} value above 24% min^{-1} survived [35]. Failure to increase PDR_{ICG} within 120 h after onset of septic shock, or a PDR_{ICG} value persistently below 5% min^{-1}, were highly associated with mortality. Furthermore, in the non-survivors, haemodynamic improvement was not associated with an increased PDR_{ICG} despite resuscitation efforts [102]. This observation further emphasises the fact that in haemodynamically stable patients, PDR_{ICG} becomes mainly dependent on the intrinsic ability of the liver to eliminate ICG, and thus may directly reflect global hepatic function.

In patients presenting with acute liver failure, accurate prognostication is important to assess the potential requirement for transplantation. However, frequently used scoring systems, such as the King's College Criteria* or the APACHE II score, are insensitive, and may fail to identify patients needing urgent transplantation [103]. Some preliminary data exist for the use of ICG elimination for estimating the prognosis of those patients. It was recently demonstrated in a small study that in adult patients assumed to have acute liver failure (n = 25), a $PDR_{ICG} > 6.3\%$ min^{-1} predicted spontaneous recovery of liver function with a sensitivity of 86% and a specificity of 89%, although most of these patients did not fulfil the criteria for true acute liver failure [104]. Nevertheless, this cut-off value supports a previous study in which PDR_{ICG} was measured in adult patients with acute liver failure after major hepatectomy who received MARS bridging therapy† [105].

These findings are consistent with those of a recent study in paediatric patients (n = 48) with acute liver failure [106]. Here, a high sensitivity and specificity were found (> 90% both) for the prediction of irreversible liver failure, and the authors determined a cut-off PDR_{ICG} value of 5.9% min^{-1} for assessing whether patients required transplantation. To date, only one study has been performed in paediatric patients investigating ICG elimination measurements, but these recent findings, together with findings in adult patients, strongly suggest benefit from routine use of PDR_{ICG} in these patients for guiding clinical decision making, and deserve further research.

Intra-abdominal hypertension is considered to be present when intra-abdominal pressure (IAP) exceeds 12 mmHg, whereas abdominal compartment syndrome is diagnosed when sustained IAP > 20 mmHg is present [107]. Several studies and one case report suggest that low PDR_{ICG} values correlate with compromised hepatosplanchnic perfusion under these circumstances [33, 108–110]. These reports suggest that PDR_{ICG} better reflects the degree of hepatosplanchnic hypoperfusion than other diagnostic methods such as central venous oxygen saturation, and, most importantly, lower PDR_{ICG} values were associated with increased mortality [33]. Another case report found that the PDR_{ICG} increased rapidly following decompression of the abdominal cavity by paracentesis [111].

In a study of 40 ICU patients, a correlation between IAP and PDR_{ICG} was demonstrated [112]. In another small study, all patients (n = 14) with an IAP > 15 mmHg had a PDR_{ICG} value < 18% min^{-1}, whereas only 70% of patients with a $PDR_{ICG} < 18\%$ had an IAP > 15 mmHg [113]. This finding suggests that in some patients, hepatosplanchnic perfusion was already compromised despite normal IAP, and that the PDR_{ICG} value may be an early marker of compromised perfusion.

Conclusion

Among patients scheduled for major hepatic resection, pre-operative assessment of ICG elimination may help in predicting development of postoperative hepatic failure, and may reduce mortality if used to limit the extent of resection. The role of ICG elimination measurement in the intra- and postoperative phases is less

* Scoring system for prognosis prediction, separating acute liver failure caused by either paracetamol overdosage or by other aetiologies. In the first group, arterial pH < 7.3 is the main predictor, whereas an INR > 6.5 is the main predictor in the latter. Other predictors include INR, serum creatinine and encephalopathy for the paracetamol overdosage group and age, serum bilirubin, time from jaundice to encephalopathy and disease a etiology for the non-paracetamol overdosage group.

† Molecular Adsorbents Re-circulation System (MARS), the most commonly used method of extracorporeal liver dialysis, designed to filter several toxins from blood. Frequently used as a 'bridge' in patients with acute liver failure who are awaiting high-urgency liver transplantation.

well defined, but it may have a role in predicting postoperative liver failure.

Evidence of benefit with the use of ICG in patients undergoing liver transplantation is even more scarce. It has been suggested that it might be used together with the MELD score to assess priority more accurately among patients on the liver transplantation waiting list. In addition, some studies suggest that PDR_{ICG} might be used to monitor graft function both intra- and postoperatively to predict the occurrence of early postoperative complications at a time when it is difficult to assess early graft function accurately using conventional tests.

Among critically ill patients, PDR_{ICG} values may predict overall mortality irrespective of the underlying disease, might help guide therapeutic strategies in patients with acute liver failure, and can be of aid in assessing the degree of abdominal hypoperfusion in case of intra-abdominal hypertension.

Overall, although ICG elimination measurements may provide useful diagnostic and prognostic information, caution is necessary when evaluating current evidence, as most of it is from retrospective cohort studies. Further prospective, randomised controlled trials of the ability of ICG elimination measurement to impact positively on outcome are required before the green light can be given for routine clinical use.

Competing interests

No external funding or competing interests declared.

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