Non-invasive liver monitoring in the critically ill: plasma disappearance rate of indocyanine green (ICG-PDR)

J. Wauters and A. Wilmer

Medical Intensive Care Unit, University Hospital Gasthuisberg, Leuven, Belgium

Abstract. In contrast to pulmonary, cardiovascular, renal and neurological function, liver function is not easily monitored in the critically ill. Traditionally, the degree of liver dysfunction is assessed by using biochemical tests - transaminases, bilirubin, albumin and prothrombin time. These are static tests, they only assess the presence of hepatobiliary injury and tend to respond late to damage. Moreover, they do not track organ perfusion, oxygenation or the functional capacity of the liver. Over the last decades, several dynamic tests have been developed that use hepatic clearance of tracer substances (indocyanine green) or metabolic capacity for certain drugs (lidocaine) as a measure of hepatic function. Recently, automatic non-invasive devices have become available which promise dynamic assessment of liver function based on indocyanine green plasma disappearance rate (ICG-PDR). This review focuses on the principles, limitations and clinical use of non-invasive liver monitoring with ICG-PDR in the critically ill. Although there is clinical evidence in favour of the prognostic use of ICG-PDR in critically ill patients, no interventions studies exist using ICG-PDR to titrate therapy. Finally, we also briefly describe some other non-invasive techniques in this context including the monoethylglycinexylidide (MEGX) test, Doppler ultrasound flowmetry and scintigraphy.

Introduction

Monitoring of organ function in the intensive care unit (ICU) is usually considered in terms of following moment-to-moment changes of relatively easily measurable parameters. Ideally, these parameters are able to detect organ dysfunction and help in guiding therapeutic interventions from the clinician, the aim being bedside titration of care. This concept is typically applied to pulmonary, cardiovascular, renal and neurological monitoring. Arterial oxygen saturation, pH, heart rate, cardiac output, blood pressure and urine output all represent critical aspects of function which are measurable and can be promptly addressed in the modern ICU. In contrast, the complexity of liver function, the inability to easily and inexpensively measure liver function and our limited ability to intervene, compromise the utility of liver monitoring.

Liver function includes the removal of substances from blood passing through its sinusoids by uptake and metabolism, synthesis and storage of new products and secretion of manufactured substances into the blood and bile. These are determined not only by integrity of liver mass, but also by perfusion (hepatic artery, portal vein) and outflow pathways (hepatic vein, bile ducts). Traditionally, the degree of liver dysfunction is assessed by using tests which reflect cellular permeability (transaminases) and excretory (bilirubin) or synthetic capacity (albumin, bilirubin and prothrombin time). These are static tests and simply assess the presence or absence of hepatobiliary injury and thus tend to respond late to damage, although evidence exists that hepatic dysfunction arises soon after injury [1][2]. Moreover, they are not useful in tracking organ perfusion, oxygenation or functional capacity of the liver over short periods of time [3]. In addition, variables evaluating the excretory and synthetic capacity of the liver are influenced by the use of plasma products. In the vast majority of cases, these tests do not adequately monitor liver function or guide therapy in critically ill patients.

Dynamic measurement of hepatic clearance of tracer substances like indocyanine green (ICG), seem to provide a more direct measure of the actual functional state of the liver. Other dynamic tests use the capacity of the liver to metabolize certain drugs (lidocaine or breath tests with antipyrine/aminopyrine) as a measure of hepatic function. These tests may provide more sensitive short-term indicators of disturbances in hepatic perfusion and function. Due to multiple interactions with inductors or inhibitors of the cytochrome oxidase system and due to a long half-life (15-35 hours), breath tests with antipyrine or aminopyrine are not suited as dynamic liver function tests in the ICU setting. Recently, automatic non-invasive devices have become available that promise assessment of liver function based on indocyanine green plasma disappearance rate (ICG-PDR) in contrast to previous more invasive liver monitoring tools requiring femoral artery or hepatic vein catheterization.

The purpose of this review is to discuss the principles, limitations and clinical use of non-invasive liver monitoring with ICG-PDR in the critically ill. In addition, we will also put into context some other non-invasive techniques such as the monoethylglycinexylidide (MEGX) test, Doppler ultrasound flowmetry and scintigraphy.

Indocyanine green plasma disappearance rate (ICG-PDR): underlying principles and limitations

ICG is a water-soluble anionic dye which is highly protein-bound after injection into the circulation. ICG is taken up almost exclusively
by the hepatocytes and is excreted unchanged into the bile without enterohepatic recirculation (Figure 1). Elimination of ICG from the blood is determined by several factors: hepatic blood flow, ATP-independent hepato-cellular uptake over the sinusoidal membrane, passage through the hepatocytes and excretion into the bile via a highly ATP-demanding transporter in the canalicular membrane. ICG has no known side effects other than a quite rare allergic reaction with an incidence of 1:40 000 [4].

In 1945, Bradley et al. described the continuous dye infusion technique to measure total liver blood flow (TLBF) based on Fick’s principle [5]. Prerequisites for validity were the placement of a hepatic venous catheter and the presence of a steady-state arterial dye concentration within a 10% range. Bradley used bromsulphthalein (BSP), but subsequently indocyanine green (ICG) was used since it exhibits, unlike BSP, almost negligible extra-hepatic removal. Many authors have validated this continuous dye infusion technique for measurement of TLBF in a wide variety of intensive care patients [6][7][8].

Later, an intravenous ICG bolus injection was used to estimate liver blood flow: TLBF = ClICG / EICG with ClICG being the hepatic ICG clearance and EICG the hepatic ICG extraction ratio, defined as the difference between the arterial (ICGart) and the hepatic venous ICG concentrations (ICGhv) over ICGart [6][7]. Decreased EICG down to 50% ten minutes after a single ICG injection made this technique unreliable for estimation of TLBF unless EICG is measured simultaneously [8][9]. Normal values of EICG are 80-90% [10]. Assuming that hepatic elimination of dye is not saturated at low doses of ICG (0.5-1.5 mg/kg) in subjects with normal EICG, elimination is flow-dependent and variations in ICG clearance directly reflect variations in hepatic blood flow [8]. Yet, impairment of hepatocellular dye captation, saturation of hepatic dye elimination or intrahepatic shunting lead to considerable lower values for EICG (20-65%) and ClICG becomes mainly dependent on hepatocellular metabolism. Without hepatic venous sampling, EICG is unknown and it is not clear whether ClICG measures hepatic blood flow, metabolic capacity or both [8][11].

Since ICG is cleared almost exclusively by the liver, intrinsic hepatic ClICG can be estimated by the systemic ICG clearance based on the systemic arterial ICG concentration after an ICG bolus injection: ClICG = C0 - CICG = C0 x e^-kt, with C0 being the initial arterial ICG concentration, k is the disappearance rate constant, t is the time after injection and T1/2 is the time at which ClICG is reduced to 50% of C0.

Figure 1. Methodology for ICG-PDR assessment (LiMON, Pulsion Medical Systems, München, Germany). After an intravenous ICG bolus injection, ICG is eliminated from the blood by hepatocellular uptake over the sinusoidal membrane, passage through the hepatocytes and excretion into the bile. The ratio of CICG to the haemoglobin concentration is assessed non-invasively by transcutaneous pulse-densitometry. ICG-PDR (%/min) is calculated as 100 x k = 100 x 0.693/T1/2. C0 is the initial arterial ICG concentration, k is the disappearance rate constant, t is the time after injection and T1/2 is the time at which CICG is reduced to 50% of C0.
some authors criticized the potential over-simplicity of the ICG-PDR assessment method. First, the mono-compartmental model used to calculate ICG-PDR does not take into account the rather complex pharmacokinetics of ICG. In fact, in both experimental animals and healthy volunteers, several authors have shown that bi- or even tri-exponential models are required to correctly describe whole-body ICG kinetics [14][15]. Second, others have reported considerable temporary redistribution of ICG into extra-hepatic extravascular tissues, in particular the kidney, leading to an overestimation of hepatic dye removal even at low-dose ICG administration [15][16].

**Indocyanine green plasma disappearance rate (ICG-PDR): from invasive to non-invasive devices and other technical considerations**

Classically, assessment of ICG-PDR relies on serial arterial blood sampling and consecutive spectrophotometric concentration analysis at certain time intervals after an ICG bolus injection (0.5 mg/kg). However, this method is both expensive and time consuming. Therefore, a fibre optic catheter-based system was developed (COLD 2-021, Pulsiom Medical Systms, Münchn, Germany) that allowed assessment of relative changes in ICG concentrations via an arterial line. This method was found to correlate well with the serial blood-sampling method [17]. More recently, a device was developed (LiMON, Pulsiom Medical Systms, Münchn, Germany) that allows for non-invasive bedside measurement of the ratio of ICG to haemoglobin concentration by transcutaneous pulse-densitometry, using the different absorption spectra of ICG (805 nm) and haemoglobin (940 nm) (Figure 1). In this way, fractional ICG-PDR (%/min) could be measured. Several studies found good agreement between non-invasively measured ICG-PDR and values obtained by the fibre optic-catheter based system or by extracorporeal photometric analysis [18]. However, some authors suggested that inaccuracy may appear when assessing ICG-PDR, non-invasively in patients with circulatory abnormalities or vasoconstriction under vasopressors, since the non-invasive method uses a technique similar to pulse oximetry [19]. Sakka et al. addressed this issue in critically ill patients receiving vasoactive drugs and reported good agreement (mean bias: 0.2 ± 2 %/min) between fibre optic and transcutaneous assessment of ICG-PDR, although all patients were haemodynamically stable [18]. A study from Faybik et al. confirmed good agreement even in situations with haemodynamic instability in patients undergoing liver transplantation with cross-clamping of the inferior vena cava [20]. With the aim of cost reduction, Sakka et al. found that an ICG bolus of reduced dosage (0.25 mg/kg) is sufficiently accurate for transcutaneous measurement of ICG-PDR in critically ill patients [21].

In normally functioning livers, up to 12 ICG doses per 24 hours can be injected, without inter-measurement influence. In patients with liver disease, ICG is detectable in the plasma up to 48 h after injection [14]. Since ICG is highly protein-bound, Keiding and Ort conducted several studies in normal pigs as well as in humans with various liver diseases concerning the influence of plasma protein on the assessment of ICG clearance [22][23]. They found that protein dilution of 25-50% (by dextran infusion) resulted in an increase of intrinsic hepatic ICG clearance of 20-40%, due to an increase of free ICG concentration. Surprisingly, an enhancement phenomenon was also described: protein dilution did not increase ICG uptake as much as it reduced the equilibrium free ligand concentration. Limited dissociation between binding protein and ICG-ligand or the influence of a water layer in the space of Disse, interfering with diffusion and ligand-binding, are suggested as potential mechanisms.

Given the good agreement between invasive and non-invasive ICG-PDR assessment and given the fact that only a limited number of studies have been published up to now using non-invasive devices, we will further make no more distinction between studies using the invasive or non-invasive techniques when reviewing the clinical use of ICG-PDR.

**Prognostic value of ICG-PDR in the critically ill**

Several authors analyzed the prognostic value of ICG-PDR in critically ill patients [1][24][25][26]. Kholoussy et al. published the first study, analysing 48 data sets of critically ill surgical patients. Although there were no significant differences in haemodynamic variables, vital signs or liver function tests between survivors and non-survivors, they found ICG-PDR to be 11.1±2.7 %/min vs. 4.8±4.3 %/min in ICU survivors and non-survivors, respectively [24]. Kimura et al. analyzed sequential ICG-PDR measurements in patients with septic shock and concluded that ICG-PDR was lower in non-survivors than in survivors both initially (within 12 hours of the onset of shock) and after 24 hours. ICG-PDR increased between 24 and 120 hours in 11 survivors but progressively decreased and remained below 5 %/min in 7 non-survivors. All non-survivors died within 2 weeks [25]. Either failure to increase ICG-PDR within 120 hours or an extremely low ICG-PDR < 5 %/min was identified as a poor prognostic sign. Sakka et al. analyzed retrospectively the lowest value of ICG-PDR during ICU admission in a wider range of 336 critically ill patients (sepsis, ARDS, cranial accident). They found that mortality increased with lower ICG-PDR values and that non-survivors had a significantly lower ICG-PDR than survivors (8.0±6.7 %/min vs. 16.7±8.6 %/min). Moreover, ROC statistics with respect to ICU survival revealed ICG-PDR at ICU admission to be as accurate as more complex scores (APACHE II and SAPS II) [26]. Malbrain et al. even found a higher area under the curve (AUC) for ICG-PDR versus APACHE II and SOFA score in a prospective multicentre study of 50 patients with severe sepsis [27]. In contrast, in a small prospective study of 27 critically ill patients with clinical evidence of inadequate tissue perfusion at ICU admission, Maynard et al. found that there were no significant differences in ICG-PDR, bilirubin, transaminases and prothrombin time between survivors and non-survivors [1].

**ICG-PDR and liver dysfunction in sepsis**

Alteration of hepatocellular metabolism has been observed during sepsis and septic shock [11]. Several authors demonstrated severe changes in $E_{ICG}$ during sepsis or SIRS (systemic inflammatory response syndrome) [9][11][28]. Wang et al. investigated hepatocyte function and ICG metabolism at different stages of the sepsis syndrome in a fluid-resuscitated cecal ligation and puncture (CLP) rat model. In early hyperdynamic sepsis (within 2 hours after CLP), they demonstrated reduced ICG extraction despite a markedly increased hepatic blood flow and microcirculation, thus suggesting depressed hepatocyte function [11]. A reduced ICG-PDR caused by compromised hepatocyte function might therefore camouflage an increased hepatic blood flow and ICG elimination then becomes flow-independent. In seven multi-trauma patients with hepatic venous catheters, Gottlieb et al. found that $E_{ICG}$ decreased from 90% on the first day after injury to 20% three days later, and then returned to 70% on
the seventh day after injury, suggesting the temporary presence of a second slower compartment of ICG clearance [9]. These decreases in \(E_{ICG}\) preceded an increase in bilirubin, suggesting that ICG clearance is an early and sensitive indicator of impaired hepatic function. Recently, Rädermacher et al. reported that ICG-PDR exhibited no significant changes during hyperdynamic porcine endotoxaemia with well maintained total liver flow, while biliary ICG declined significantly [28]. Several reasons may explain these findings. Overestimation of ICG-PDR may be present because of lower dye protein binding due to decreased plasma protein content following aggressive fluid resuscitation. Moreover, others have reported temporary extra-hepatic ICG redistribution, in particular in the kidney.

The authors hypothesized that accumulation of ICG in the liver with prolonged ICG storage could be present, due to endotoxin related downregulation of the energy-demanding excretory transport mechanism [28][29]. Since bile was collected only 1 hour after ICG injection and intrahepatic ICG concentrations were not measured, this hypothesis could not be proven. All together, Rädermacher concluded that ICG-PDR failed to accurately reflect hepatocyte dysfunction and short-term biliary ICG excretion and thus that normal values of ICG-PDR should be interpreted with caution in early, acute inflammatory conditions. Mizushima et al. reported a lower ratio of effective hepatic blood flow to cardiac output (EHBFCO) in 13 septic ICU patients (APACHE II = 23.3) than in 16 non-septic ICU controls (APACHE II = 12.8), suggesting inadequate splanchic perfusion or metabolic changes [30]. Again, the methodology can be questioned since EHBF was calculated based on ICG-PDR, without taking into account \(E_{ICG}\).

**Effect of therapeutic interventions on ICG-PDR and titration of therapy**

To be able to guide therapy, ICG-PDR first needs to prove to be a sensitive and fast-responsive indicator of liver perfusion and function following therapeutic interventions. Although it is still not clear whether ICG-PDR assesses hepatic perfusion or metabolic liver function, several small human and animal studies evaluated the effect of therapeutic interventions on ICG-PDR. These studies might give at least a partial answer to this question.

Some studies assessed the effect on ICG-PDR of short-term “mechanically-induced” modulations, expected at first to influence only liver perfusion. Hofmann et al. increased cardiac index from 2.8 to 3.5 l/min/m² by fluid loading (630 ml hydroxyethyl starch) in 12 haemodynamically stable post-cardiac surgery patients and found no significant changes in ICG-PDR one hour after fluid loading, although ICG-PDR increased in five patients with an initial ICG-PDR less than 18 %/min [31]. In another study of 24 patients, pre-operative administration of crystalloid (1000 ml over 9 h) resulted in an increase of hepatic blood flow, as estimated by the clearance of an ICG-bolus, in comparison with 24 starved controls [32]. Since cardiac index was similar in both groups, decreased hepatic vascular resistance might account for this finding.

Several authors described the effects of applying external pressures (PEEP or elevated intra-abdominal pressure) on ICG-PDR [33][34][35][36][37]. Pressure-controlled ventilation in 25 patients after orthotopic liver transplantation with changing PEEP levels up to 10 cm H₂O did not change ICG-PDR, even in those with marked CI decrease (from 5.0 to 3.5 l/min/m²) [33]. The authors hypothesized, in accordance with the findings of Matuschak et al. [34], that the PEEP-induced decrease in CI and hepatic flow is counterbalanced by a higher hepatic ICG extraction. The underlying mechanism may be the increased trans-sinusoidal ICG passage into the extracellular space of the liver with prolonged sinusoidal passage time and the enhanced ICG uptake because of PEEP-induced elevation of back-pressure to hepatic venous outflow. Kiefer et al. used the primed continuous infusion of ICG with hepatic vein catheterization to measure total hepatosplanchnic blood flow and ICG extraction separately but found no changes after a PEEP increase of 3-5 cm H₂O [35]. Adequate fluid resuscitation and a rather small increase in PEEP are probably responsible for these findings. Others applied elevated intra-abdominal pressure (IAP) by prone positioning patients with acute lung injury [36][37]. Michelet et al. found that ICG-PDR decreased from 17.5 to 14 % in parallel with raising IAP (from 7 to 15 mmHg) in patients prone-positioned during 6 hours on a conventional foam mattress, while an air-cushioned mattress prevented these changes [36]. Biochemical liver function did not change in both groups. In a similar study, Matejovic et al. confirmed these findings in patients on an air-cushioned mattress, assessing hepatosplanchnic blood flow by the more validated continuous ICG infusion method with hepatic vein catheterization [37]. Functional and metabolic markers such as liver lactate clearance or ICG extraction also remained unchanged. In a rabbit model, Nakatani et al. found that, at an IAP of 20 mm Hg, a slight decrease in ICG-PDR did not affect hepatic energy level, while at 30 mm Hg, a firm decrease in ICG-PDR was associated with a reduced hepatic energy level without hypoxaemia [38].

Pharmacological modulations were also used to assess the effects on hepatic ICG handling. Rokytà et al. observed an increase in total hepatosplanchnic blood flow (continuous ICG method), proportional to cardiac index, in response to the initiation of post-pyloric enteral nutrition in haemodynamically stable septic ICU patients [39]. Hepatic metabolism (lactate/pyruvate ratio) remained unchanged. In 20 patients with septic shock, Lehmann et al. found that a continuous infusion of the prostacyclin analogue iloprost, known as a vasodilator and an anti-inflammatory agent, reversibly improved ICG-PDR with 18% after one hour and 35% after 24-hour infusion, without any change in volume status, cardiac index (CI) or blood pressure. One hour after the end of the infusion, ICG-PDR returned to baseline values. The fast changes suggest a perfusion effect, although gastric tonometry did not change simultaneously. The additional delayed effect may also suggest an effect resulting from improved liver function, but biochemical data on liver function were not provided [40]. Kiefer et al. confirmed these findings; infusing iloprost over 90 minutes increased splanchic blood flow without changes in metabolic capacity [41]. In contrast, Devin et al. could not show any change in ICG-PDR in 15 haemodynamically stable patients with hepatic dysfunction after liver transplantation or decompensated liver cirrhosis one hour after a prostacyclin infusion, although CI increased significantly from 5.4 to 6.1 l/min.m² [42]. The reason for the different results in the latter two studies is unclear. In accordance with others, Joly et al. did not find any measurable change in ICG-PDR after a 1-hour dobutamine infusion in 14 patients with septic shock [43][44]. A 1-h infusion may have been too short to observe changes in ICG elimination by hepatocytes, but more plausible is the fact that a dobutamine related increase in hepatic blood flow is masked by a profound hepatocellular dysfunction that impedes ICG excretion, ICG-PDR becoming then flow-independent. In 25 ICU patients with systemic inflammatory response syndrome (mean APACHE II score of 22), Maynard et al. found that low-dose doxepamine increased

---

**Netherlands Journal of Critical Care**

**Volume 11 • No 2 • April 2007**

95
splanchnic blood flow as measured by ICG clearance without any change in systemic haemodynamics. Although $E_{\text{ICG}}$ was not measured, a parallel improvement in MEGX formation from lidocaine was observed [45]. Other studies have revealed either no change or an improvement in hepatic haemodynamics and hepatocellular function after treatment with norepinephrine [46].

To the best of our knowledge, no study has yet been published that used ICG-PDR as a real titration parameter for therapy, which may not be surprising taking into account the former results. However, in patients with early allograft dysfunction (EAD) after liver transplantation, ICG-PDR ($< 10\%$ within 72 hours after reperfusion) has recently been included in the criteria to start up molecular adsorbent recirculatory system therapy (MARS) [47]. Unfortunately, study design did not allow the conclusion whether addition of ICG-PDR to the inclusion criteria resulted in better results.

**ICG-PDR after liver transplantation or hepatectomy**

The clinical value of ICG-PDR has also been studied in liver transplantation, for the evaluation of donor organs or to determine the extent of resection in liver surgery. Several authors studied the predictive capability of ICG-PDR on graft quality and clinical outcome and suggested ICG kinetics cut-off values to predict graft dysfunction in orthotopic liver transplantation (OLT) [48]. In 50 patients following OLT, Tsubono et al. showed that ICG-PDR on postoperative day 1 was a better predictor of liver-graft related outcome than any of the conventional liver function tests [48]. Furthermore, ICG-PDR showed significant correlation with the severity of preservation injury, longer ICU and hospital stay, prolonged liver dysfunction and septic complications. Data from Hori et al. from post-transplant patients revealed that ICG-PDR correlated strongly with graft parenchymal damage on liver biopsy within four weeks after transplantation [49]. Wesslau et al. found in 41 organ donors that livers with lower ICG-PDR values (cut-off 15%/min) were associated with higher rates of discarded grafts [50]. The ICG test has also been used successfully to medically determine the functional capacity of diseased livers and to predict the outcome of patients with liver abnormalities before and/or after major hepatic resections e.g. in cirrhotic patients with hepatocellular carcinoma [51]. In this context, Hashimoto et al. showed that ICG-PDR correlates well with the liver parenchymal cell volume, as calculated based on a preoperative computed tomography scan and a liver specimen resected peroperatively in a mixed patient population (normal liver and liver cirrhosis) [52].

**Indocyanine green plasma disappearance rate (ICG-PDR): validation against other techniques**

Pulsed doppler ultrasound flowmetry and contrast ultrasound

Pulsed doppler ultrasound (US) flowmetry allows the quantification of portal venous and/or hepatic arterial blood flow non-invasively. Obviously, this technique is limited by reproducibility problems and can only estimate changes in blood flow, since correct measurement of absolute regional blood flow crucially depends on correct assessment of blood vessel diameter and velocity, which is difficult with large angles of insonation. However, pulsed doppler US has been shown to successfully predict changes in ICG clearance following food intake in healthy volunteers [53]. Although the use of contrast ultrasound with intravascular contrast agents to assess liver perfusion is growing fast, we could not find any study comparing dynamic liver function tests (ICG, MEGX) and contrast US.

$^{99m}$Tc-GSA liver scintigraphy

Asialoglycoprotein receptors (ASGP-R) on hepatocytes are characteristic of functional liver cells and $^{99m}$Tc-GSA (as a ligand for ASGP-R) has been used as a reliable marker for hepatic functional reserve and functional hepatic volume. Several studies have demonstrated correlations between ICG-PDR measurements and $^{99m}$Tc-GSA liver scintigraphy in patients with chronic liver disease, after hepatectomy and post liver transplantation [49][54].

**MEGX (monoethylglycinexylidide) test**

Another commonly used approach for the evaluation of liver function is based on the hepatic metabolism of lidocaine to monoethyglycinexylidide (MEGX) by the drug-metabolizing enzyme P450. Although lidocaine has a high extraction ratio in normal livers, making its conversion mainly flow dependent, extraction ratio may be very variable in the critically ill, making it difficult to know whether the MEGX test is measuring predominantly hepatic blood flow or hepatocyte function [55]. Measurement of MEGX formation is done by immunoassay after taking blood samples before and after lidocaine injection. The mean MEGX concentration in healthy volunteers is $97 \pm 12$ ng/ml and less than $50$ ng/ml is thought to represent significant hepatic dysfunction [56]. The response of the MEGX test after therapeutic interventions seems to parallel that of the ICG-PDR and gastric mucosal pH in critically ill patients [1][57][58]. However, the response of the MEGX formation rate may substantially differ from that of other hepatopancreatic metabolic pathways due to intrahepatic metabolic compartmentalisation [59]. Moreover, several other important limitations exist: since MEGX formation uses P450, it could be influenced by medications regularly used in the ICU: immunosuppressants, anti-epileptic drugs, proton pump inhibitors and antibiotics [56][60]. Propofol also interferes with lidocaine metabolism [61]. Finally, the rate of MEGX formation can also be affected by extrahepatic lidocaine metabolism [62].

**Conclusion**

Since the introduction of non-invasive, bedside liver monitoring based on ICG-PDR, this technique is being increasingly used as a means to evaluate liver function in the critically ill. However, the absence of a hepatic venous catheter results in severe limitations in interpretation of ICG-PDR values: ICG-PDR is not able to distinguish between changes in hepatic blood flow or hepatic metabolic or excretory function.

Good clinical evidence exists concerning the use of ICG-PDR as a valuable prognostic parameter in the setting of critically ill patients and liver transplantation. Moreover, they seem to be able to detect hepatic dysfunction in the absence of overt biochemical abnormalities. Although several small studies have described the effects of therapeutic interventions on ICG-PDR, at this point no clinically valuable intervention studies relying on ICG-PDR exist. Depending on the intervention, rapid changes in time of ICG-PDR are probably due to changes in hepatic blood flow. But, before ICG-PDR can be considered as a real parameter to monitor liver function non-invasively in the critically ill patient, further studies should use ICG-PDR together with other clinical variables for titration of therapy.
References


