Clinical Use of Indocyanine Green (ICG) Kinetics in Liver Anaesthesia and ICU

13

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13.1 Notes on Liver Anatomy and Physiology

The liver is the largest visceral organ, weighing, in healthy adults, between 1,500 and 1,600 g: it has two anatomical lobes (left and right) separated by a reflected surface of peritoneum (falciform ligament) [1]. Instead, from the surgical point of view, the porta hepatis, point of division of the hepatic artery and portal vein into right and left branches, is the reference point for the division. Based on the branches of portal and hepatic veins, the two lobes are divided into eight segments, allowing the definition of the various types of hepatic resection (Couinaud) [1, 2] (Fig. 13.1).

The *hepatic lobule* is the anatomical and functional unit of the liver. It has the shape of a polygonal (hexagonal) pyramid with an apex trunk of 1 mm in diameter and a height of about 1.5–2 mm, delimited by a layer of connective tissue (reticular connective). Each lobule is formed by numerous cellular laminae consisting of hepatocytes; the plates are perforated and anastomosed with each other and define a system of irregular vascular spaces: the *hepatic sinusoids*. The cellular edges and capillaries show a radial arrangement converging from the periphery toward the centre of the lobule. The axis of the lobule is occupied by the centrilobular vein, tributary of the hepatic vein, within which the sinusoids open up. The area where three or more adjacent lobules are in contact with each other is called a *portal space* ('portal triad', containing a bile duct, a terminal branch of the hepatic artery and the portal vein). Metabolic zones form the hepatic acinus [2]. *Zone 1* is the periportal zone, is centred around the portal triad and, being close to the hepatic artery, is oxygen rich. It is more resilient to hemodynamic stressors, least susceptible to necrosis and first to regenerate. These zones are involved in gluconeogenesis/

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Fig. 13.1 Liver segmental anatomy (From Mulaikal and Edmond [2])
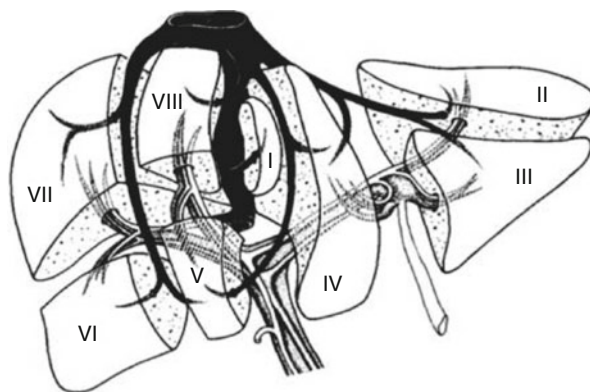
glycogenolysis. *Zone 3* is the pericentral or perivenous zone, very close to the central vein: it has the lowest oxygen tension. This zone is highly susceptible to stressors, hypoxia and is the last to regenerate. Zone 3 is the site of drug detoxification and phase 1 and 2 metabolism [2].

The liver has a dual blood supply, which includes an arterial system (hepatic artery, HA) and a venous system (portal vein, PV). The total liver blood flow is approximately 1,500 ml/min (100 ml/min/100 g). The hepatic artery flow is approximately 300 ml/min (30 % of total hepatic flow, 45–50 % of total oxygen intake), while portal vein is usually estimated between 1,000 and 1,200 ml/min (70 % of total blood flow, 50–55 % of oxygen supply). The O_2 hepatic extraction, normally less than 40 % (4–6 ml/100 g/min), is increased in case of increased demand [2].

Both the terminal portal venules and the terminal hepatic arterioles end in the hepatic sinusoids, through which the entire afferent hepatic blood flows before reaching the efferent vascularisation (terminal hepatic venules). Hepatic blood drainage is via the hepatic veins (right, left, middle) which drain into the inferior vena cava.

The portal system is a low-pressure (5–12 mmHg)/low-resistance system: the gradient between portal vein and hepatic vein (HVPG) ranges between 1 and 5 mmHg: portal hypertension is defined as a pressure of >12 mmHg or for a portal vein–inferior vena cava (IVC) gradient >5 mmHg. The arterial system has a high level of resistance and a high flow. Hepatic blood flow and distribution are dependent on hepatic arterial resistance, intrahepatic portal resistance and portal flow. Intrinsic and extrinsic mechanisms regulate the hepatic blood flow. Among the extrinsic factors, sympathetic innervation plays an important role in controlling vascular tone (adjusting the capacitance of the uptake capacity of circulating blood). Within the hepatic arterial bed, both alpha (alpha 1 and 2) and beta (beta 2) receptors are represented, while only alpha receptors are present in the portal vein. Dopaminergic receptors are present in both vessels. Vasopressin, able to increase the hepatic artery resistances, reduces the PV resistances, thus playing a relevant role in the treatment of portal hypertension. Maintaining a constant hepatic inflow is crucial to optimise drug metabolism and synthetic functions. Self-regulating mechanisms, present in the hepatic artery, are not demonstrated in the portal vein.

Among the intrinsic factors (working independently of humoral neuroregulation) are self-regulating mechanisms for flow/pressure: in case of critical drop in blood pressure, arterial hepatic blood flow is maintained until systolic arterial pressure falls below 75–80 mmHg, via reduction of resistance mechanism. In case of reduced portal flow, hepatic artery flow increases, buffering the changes in portal flow (*hepatic artery buffer response*, HABR). In a situation of critical drop in portal flow (flow reduction of 20–30 %), there is an increased vicarious flow in the hepatic artery (increase up to 100 %) in order to maintain the hepatic blood supply. The mechanism is supported by the reduction of adenosine washout (present with normal portal flow, but missed in the presence of low flow) followed by hepatic artery vasodilatation. A portal flow counterbalance in the presence of hepatic artery occlusion does not seem to exist. Instead, there is an increased hepatic arterial resistance with flow reduction in case of elevated hepatic venous pressure [1, 2].

The liver performs many functions such as protein synthesis; uptake, storage and metabolism (biotransformation and degradation) of endogenous and exogenous substances (among them carbohydrates, lipids, proteins, hormones, drugs); bile production; and immune defence with different mechanisms, mainly operated by the Kupffer cells (KC, so-called fixed hepatic macrophages, 80–90 % of the reticular endothelial system, 10 % of the entire liver cell mass), responsible of phagocytosis (bacteria, fungi, viruses, immune complexes, antigens), clearance of endotoxin and secretion of mediators capable of adjusting microcirculatory hepatic protein catabolism. Due to the indeed wide variety of processes the liver is involved, no single parameter or test able to measure all components simultaneously has been available so far [1–4].

13.2 Static and Dynamic Liver Function Tests [1–5]

To assess liver function, static (also called conventional tests) and dynamic tests are available [3–5]. The static tests track the different functions separately, and, in the event of injury, they might describe its size: these tests are, since long, part of scoring systems, able to track chronic (Child–Pugh; MELD) or acute (SOFA) functional impairment of the liver. However, static tests are not able to predict the quality and the extent of the functional recovery of the liver (or of a newly grafted liver), as they essentially show a 'frozen' (*static*) representation of the integrity (or not) of hepatocytes and of metabolic and synthetic pathways (Fig. 13.3). Metabolic function includes enzymes of the cytochromes (*phase 1*) and the phase of glucuronide conjugation (*phase 2*). Bilirubin, derived from haemoglobin catabolism, expresses the capacity of uptake, conjugation and excretion in the bile of haeme (breakdown product of haemoglobin; 1 g Hb leading to 36 mg bilirubin). After uptake by the liver cell, the haeme is exposed to glucuroconjugation (metabolic phase 2) for solubilisation, aimed at excretion in the bile: the process can be relatively insensitive to ischaemic insult, at least in the early stages. In general, hyperbilirubinaemia depends on haemolysis (pre-hepatic disease), cell damage or reduced intrahepatic bile excretion (cholestasis). Albumin, vitamin K-dependent

coagulation proteins (factors II, VII, IX, X; protein C; protein S; and protein Z), factor V, fibrinogen, antithrombin, alpha 2 plasmin inhibitor, and plasminogen represent the (elevated) share of synthetic activity of the liver. The short half-life of FV (4 h) and FVII (4–6 h) might quantify the liver damage in acute liver failure and is used in the Clichy criteria, together with the presence of hepatic encephalopathy, to indicate LTx for FHF [6].

13.3   Liver Enzymes, Liver Function and Liver Injury [4, 5]

AST (*aspartate aminotransferase*) and ALT (*alanine aminotransferase*), present in various organs, have an important role for the metabolism of amino acids. AST is less specific, being present at cardiac and muscular level. ALT is more liver specific, is highly represented in the cytoplasm and is, for the most part, in the periphery of the liver lobule: moderate increase is reported in case of centrilobular hypoxia. In the presence of acute hepatic injury (acute hepatitis), the serum concentration of ALT, mainly represented in the periportal areas of the liver, increases significantly, as a consequence of increased permeability of the cell membrane or necrosis. Increased AST/ALT is associated with ischaemic injury and its size (liver injury), but does not provide information on functional hepatic impairment and therefore is considered inferior to dynamic tests when assessing hepatic functional reserve [3–5]. *Alkaline phosphatase* (ALK) and *gamma-glutamyl transferase* (GGT) are mainly used to quantify cholestasis. *Lactate dehydrogenase* (LDH, mainly fraction 5) is a rather nonspecific index of ischaemic liver (but not only!).

Dynamic tests [3, 7] are related to the ability of the liver to metabolise or eliminate substances. Unlike conventional tests, dynamic tests are able to assess liver function within a relatively short time span, are repeatable in relatively short time and may confidently provide a reliable and more global prognostic assessment (Fig. 13.2). Among them are ICG clearance, caffeine test, BSF clearance, amino acid clearance, galactose elimination capacity, formation of *monoethylglycinexylidide* from lignocaine (MEGX test) and aminopyridine test.

- The aminopyrine breath test measures the microsomal metabolical capacity of the liver cell. The test is based on demethylation and subsequent metabolism of ^{14}C-aminopyrine marked by the microsomal enzyme cytochrome P450 dependent. The extent of demethylation is measured indirectly by the exhaled CO_2.
- Galactose elimination capacity (depending on cytosolic mitochondrial function) studies the function of the liver cell. Metabolisation occurs through phosphorylation by the galactokinase. The test is complex in clinical practice since it requires samples over 20–50 min and presents false positives in relation to fasting and liver regeneration.
- Monoethylglycinexylidide (MEGX) is a derivative of lidocaine metabolism and is related to the activity of cytochrome P450. It has been used in the past (and still by some) in liver surgery (value >25 ng/ml predicts safe liver resection) and as a prognostic indicator in patients candidate for liver transplantation. The results
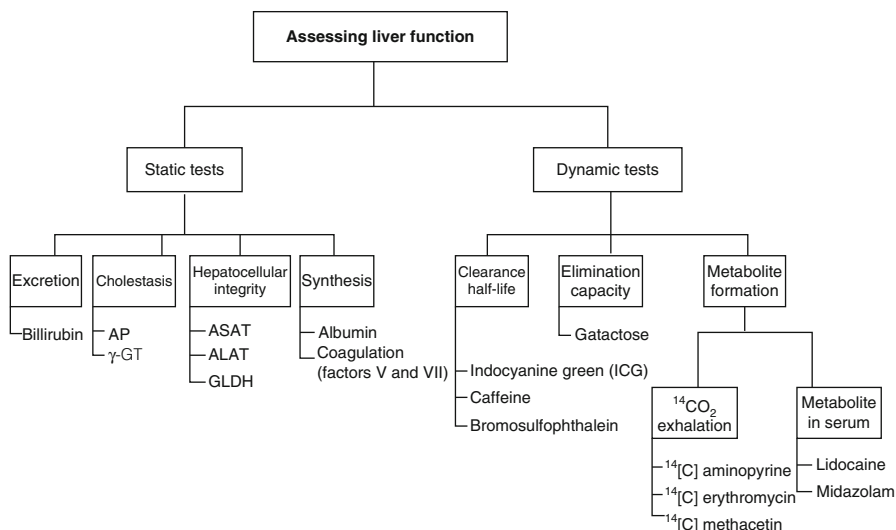
Fig. 13.2 Static and dynamic assessment of liver function (From Sakka [3])

can be altered by interaction with other drugs that affect the cytochrome P450. The test, performed in the laboratory and whose results are not obtained in real time, has not been used in the field of anaesthesia and ICU.

13.4 The Clearance Principle: Liver Function and Hepatic Perfusion [8]

Most quantitative liver function tests rely on the clearance principle: the hepatic clearance (Cl) is the product of flow (Q) and hepatic extraction (Ex).

$$Cl = Q \times Ex \tag{13.1}$$

According to this principle [8], substances are classified at high or low hepatic extraction rate. In case of drugs at *high extraction rate*, liver blood flow becomes the limiting factor, and clearance will approach liver blood flow. Instead, *low extractable compounds* are flow independent: in this case, the hepatic clearance is the measure of the metabolism and/or elimination process, or more precisely, it represents the intrinsic ability of the liver to remove substances without flow limitation, i.e. the intrinsic hepatic clearance. Equation 13.1 can be rewritten as

$$Cl = (Q \times Clint)/(Q + Clint) \tag{13.2}$$

Then, according to Imamura et al. [8], the measure of clearance of compounds with high extraction rate is an indicator of *liver blood flow*, while the clearance of low extractable substances represents *intrinsic clearance* (*Clint*). In healthy subjects, with very high extraction, indocyanine green (ICG) clearance is considered a

surrogate of hepatic blood flow; on the contrary, in cirrhotic patients, due to the reduced hepatic extraction secondary to the disease, ICG clearance represents the intrinsic clearance, characterised by a reduced uptake: steady-state hemodynamic conditions are mandatory to adequately assess liver function.

13.5   Indocyanine Green Clearance: The Tests

Among the dynamic tests, *indocyanine green* (ICG) clearance remains the most relevant, widely used in clinical practice today both in the surgical and medical critically ill patient [9–12]. ICG is a fluorescent, water-soluble, inert, tricarbocyanine with a very high hepatic extraction (70–80 %) and a very low toxicity (the side effects described are very rare, about 1/40,000): the only known contraindications are allergy (non-immunological histamine release), iodine allergy or thyrotoxicosis, the latter due to the presence of iodine in the molecule. Since 1960, its elimination rate has been largely used to measure liver function and hepatic blood flow [13–15]: in the late 1990s, Lau had shown the superiority of ICG clearance (ICG_{Cl}) compared to the aminopyrine breath test and the clearance of amino acids as a predictor of mortality in patients undergoing liver resection [15]. Important applications are now available in liver resection surgery, in liver transplantation and in intensive care [3, 9–11]. The conventional measurement of ICG_{Cl} requires serial blood sampling after ICG injection. Ex vivo photometric analysis of consecutive arterial blood samples after intravenous bolus injection is the gold standard; however, being a time-consuming and complex procedure, it has now been abandoned in favour of the more recently developed monitors that allow transcutaneous noninvasive pulse dye densitometry (PDD) tests at the bedside (LiMON, Pulsion, Germany; DDG-2001 Nihon Kohden, Japan) [9–11]. Available monitors express ICG elimination in terms of the ICG plasma disappearance rate (ICG_{PDR}) or retention rate at 15 min (ICG_{R15}), since only relative ICG concentration changes have to be assessed (Fig. 13.3).

The results of ICG elimination measured by the PDD method have been shown to correlate with those obtained by the invasive method used in critically ill patients (whether or not haemodynamically stable) and in patients after liver surgery. Both devices calculate the rate constant (k) of the ICG indicator–dilution curve using backward dynamic extrapolation of the elimination phase [9]. Appropriate calculations using K value allow the determinations of functional parameters able to quantify liver function. The ICG kinetics have been studied since 1960 in animals and humans to measure blood flow, cardiac output and circulating blood volume and, later, to assess liver function [9–11]. Due to high hepatic extraction (70–80 %), ICG clearance has been used as an index (measure) of liver blood flow. The usual ICG dose of 0.5 mg/kg generates in the average subject an initial plasma concentration of 100 mg/ml: according to Sakka, however, reliable results are also available using 0.25 mg/kg [3]. Once injected, ICG shows a very high protein binding (95 % to albumin, alpha1 lipoproteins and beta lipoproteins) and a very short half-life (3–5 min) [9–11]. It distributes uniformly and rapidly (2–3 min) in the blood, with a volume of distribution approximately equal to that of plasma. ICG is almost entirely

Fig. 13.3 ICG indicator dilution curve. *ICG* indocyanine green, *C ICG*, ICG blood concentration. *A* Primary peak, *B* secondary peak (recirculation phase), *C* (hepatic) elimination phase (From Vos et al. [9])
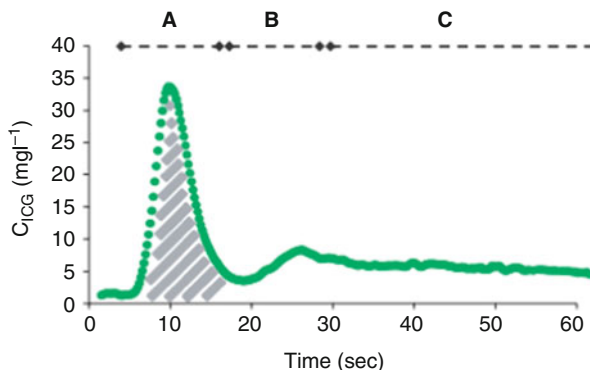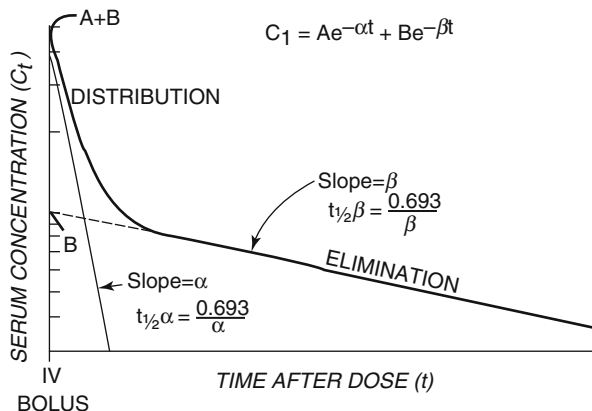

extracted by the liver (uptake across the sinusoidal plasma membrane) and transported within the liver cells by transporting polypeptides (1 B3 and Na-taurocholate cotransporting polypeptides). It is excreted unchanged almost exclusively into the bile in nonconjugated form with neither metabolism nor enterohepatic recirculation, carried by the ATP-dependent export pump multidrug resistance-associated protein 2 (MDRP2) and multidrug resistance P-glycoprotein (MDR3), reflecting hepatic excretory function and hepatic energy status [9–11]. Then two processes are involved in hepatic ICG clearance: sinusoidal uptake and canalicular excretion, the former playing the most important role in humans. Due to the very high hepatic extraction, ICG clearance is, in normal conditions, hepatic blood flow limited. After the intravenous bolus administration, the ICG dilution curve shows (i) a primary peak (used to calculate cardiac output); (ii) a second elimination peak (recirculation phase), sometimes followed by smaller peaks, used to estimate circulating blood volume; and (iii) an (hepatic) elimination phase, lasting 10–20 min [9].

In the dye dilution time curve, two components are recognised [8]: (a) the *distribution* phase, representing ICG removal from the plasma, due to the uptake by the liver cells; and (b) the *elimination* phase in the bile (97 % of the entire elimination process) (Fig. 13.4).

The decay is bi-exponential, with linear kinetics up to a dose of 1 mg/kg. The ICG hepatic clearance therefore depends on hepatic blood flow and transporter capacity: signs of liver dysfunction as indicated by impaired clearance of ICG (see below) may depend on reduction of blood flow, on impaired cellular function, or on both (blood flow clearance and transporter capacity). ICG half-life is substantially prolonged in the case of liver disease. Different from the usual two-compartment model, ICG is excreted from the peripheral compartment (the liver) and not from the central compartment (plasma). According to this model, the initial rapid fall in concentration, called the *distribution phase*, represents the uptake of ICG from the plasma by the liver; the subsequent relatively slow fall, called the *elimination phase*, represents the elimination of ICG from the liver into the bile. The transition from the distribution phase to the elimination phase of ICG occurs approximately 20–30 min after the administration. ICG_K (min^{-1}) is usually determined from the first 15-min component of the ICG disappearance curve.

Fig. 13.4 Graphic representation of ICG kinetics (From Imamura et al. [8])

$$C_1 = Ae^{-\alpha t} + Be^{-\beta t}$$

A+B

DISTRIBUTION

Slope=β

$t_{1/2}\beta = \dfrac{0.693}{\beta}$

ELIMINATION

B

Slope=α

$t_{1/2}\alpha = \dfrac{0.693}{\alpha}$

SERUM CONCENTRATION (C_t)

IV BOLUS

TIME AFTER DOSE (t)

The ICG transport capacity may be reduced either because of the downregulation of organic anion-transporting polypeptides [4] or by competitive inhibition due to hyperbilirubinaemia [16]. With respect to the former, cytokines such as tumour necrosis factor-α (TNF-α) and interleukin 6 (IL6), released by Kupffer cells in patients with steatosis and/or hepatic injury (hepatitis), are able to affect the expression of organic anion-transporting polypeptide isoforms and sodium taurocholate cotransporting polypeptide, thereby affecting ICG uptake by the liver. Bilirubin and ICG share the same enzyme transport system (ATP export pump MDRP2), making high the chance of altered results (false pathological values) in the presence of hyperbilirubinaemia (vide infra) [9, 16, 17]. Consequently, the ICG test may be of limited value in patients with a condition of global hepatocellular dysfunction and in the case of hyperbilirubinaemia (generation of false poor results) [9, 10]. At the opposite site are high flow states, able to mask an altered excretory function and providing false-reassuring results (better than expected liver function), due to the generation of false 'normal or near-normal' results [10]. It has been documented that ICG_{Cl} is not adequate to measure hepatic blood flow in specific clinical settings: for example, the fraction of hepatic extraction (70–80 % in healthy subjects) is greatly reduced in cirrhotic patients (20–30 %), making ICG_{Cl} a representation of Cint (uptake clearance; *see above*) [18]. Studying ICG kinetics in patients with cirrhosis, Kawasaki et al. [19] reported significant alterations of uptake and release constants (k) (but the release constant is questioned by other authors). Instead, the constant of elimination of ICG in the bile seems to be normal. In the same study, measuring hepatic blood flow with the galactose clearance test, it was shown that in cirrhotic patients, the reduction of ICG_{Cl}, expressed as ICG_{R15} (the circulatory retention of ICG 15 min after bolus injection, vide infra), does not (only) depend on hepatic blood flow reduction but also on a reduced extraction of the liver cells. In cirrhotic patients, this phenomenon seems to be related to the extent of the sinusoidal capillarisation and to the presence of intrahepatic shunts [9, 19, 20]. In normal conditions, substances (including proteins) diffuse freely between the sinusoids and hepatocytes. As sinusoid capillarisation develops, diffusion of these substances

becomes impaired and barrier limited, as is in the capillaries of other districts. Due to its high protein binding, ICG is very sensitive to the sinusoidal capillarisation. Figure 13.6 shows the disappearance of ICG from plasma in normal subjects (full signs) and cirrhotic subjects (empty signs). According to Imamura, in cirrhotic patients, ICG_K and ICG_{R15} might reflect the degree of sinusoidal capillarisation, intrahepatic shunts and, in part, reduced liver blood flow [19].

The logarithmic transformation of the curve in the distribution phase allows the measurement of different parameters that quantitatively assess the removal of ICG by the liver cells [9, 10].

1. *Constant K* (ICG_K) – disappearance rate constant or elimination rate constant
2. *Clearance* of green indocyanine (ICG_{Cl})
3. *Plasma disappearance rate* (ICG_{PDR})
4. *Retention rate at 15 min* (ICG_{R15})

In clinical practice, ICG_{PDR} and ICG_{R15} are the ICG kinetic parameters most frequently used to dynamically assess liver function [9, 10] (Fig. 13.5):

1. *ICG_{PDR} – plasma disappearance rate*
   (a) Reduction of ICG blood concentration expressed as the percentage change over time, starting (time 0) from a concentration of 100 % (normal values >18 %/min). The method, having satisfactory correlation ($r^2 = 0.77$) with ICG_{Cl}, is validated as a surrogate for clearance in the critically ill)
       (i) $PDR(\%/min) = \ln 2/t\frac{1}{2} \times 100$ ICG_{PDR} might represent, at variance of ICG_{R15}, ICG uptake by hepatocytes, its excretion into the bile, blood flow-dependent liver metabolism and energy status [21]
2. *ICG_{R15} – retention ratio after 15 min*
   (a) The relationship between the concentration of ICG at 15 min and initial concentration (normal <10 %)
       (i) $R15 (\%) = C_{ICG15}/C_{ICG\ T0} \times 100$
           Assuming an initial plasma concentration of 100 mg/ml (0.5 mg/kg ICG in a subject with a plasma volume of 50 ml/kg BW), ICG_{R15} can be determined by transforming the ICG concentration curve to a 'point

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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: $C_{ICG} (t) = C_0 * e^{-kxt}$	> 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}).

Fig. 13.5 Variables to quantificate ICG kinetics (From Vos et al. [9])

zero' (100 %) and then describing the decay (at min 15) as percentage change per time (%/min) in a logarithmic graph, seen as a negative slope. According to Imamura, as the assumption of the initial concentration of ICG is correct, ICG_{R15} is pharmacologically equivalent to ICG K, and it has been widely used as an alternative to ICG_K for its convenience [8]. It might represent the hepatic blood flow.

3. *ICG plasma clearance* 500–700 ml/min/m^2

   (i) It depends on hepatic blood flow, liver function and bile flow. It describes the volume of blood completely purified by ICG in the time unit.

ICG_{PDR} and ICG_{R15} are the two sides of the same phenomenon: ICG_{PDR} reads the disappearance of ICG from plasma (% per min) and ICG_{R15} the amount of ICG remaining in circulation 15 min after the administration. However, these tests are used in the literature in a different (and potentially confounding) manner. ICG_{R15} is mainly used in the evaluation of the functional reserve of the liver in case of hepatic resection in cirrhotic patients [8, 11], ICG_{PDR} and ICG $_{R15}$ in the assessment of liver graft function [22] and PDR and clearance in critically ill patients [3, 21].

As mentioned above, *plasma disappearance rate* (ICG_{PDR}) and *retention rate at 15 min* (ICG_{R15}) are calculated using either the conventional invasive method or, more recently and more simply, a noninvasive method (pulse dye densitometry (PDD) and spectrophotometry) [9–11]. The conventional invasive method involves the construction of the dilution curve by measuring the concentration of ICG in plasma by spectrophotometry of various arterial blood samples taken at defined times: it has been used in many studies dealing with functional assessment of the liver even in recent times [19]. However, this method is expensive and difficult to implement in clinical practice. In the 1990s, it was possible to measure PDR through a fibre-optic catheter placed in the femoral artery and connected to a computer (COLD System, Pulsion) which allowed, together with the measurement of PDR, the study of volumetric haemodynamics [23]. As already mentioned, the noninvasive method relies, instead, on the measurement of ICG concentrations using PDD and spectrophotometry via an optical transcutaneous pulse spectrophotometric sensor (DDG-2001 Nihon Kohden; LiMON, Pulsion) [11, 24–26]. Pulse dye densitometry measures the concentration of ICG in blood based on the principle of the difference in absorption of the light wave with two different frequencies: 805 nm (absorption frequency of the peak of ICG) and 905 nm (frequency at which ICG has no absorption); the principle is analogous to the mechanism of absorption of the difference between oxyhaemoglobin and reduced haemoglobin. There is no influence of haemoglobin, whether oxidised or reduced, absorption being very low at the frequency wave used for ICG. The same is true for bilirubin (absorption peak at 470 nm) [9, 10]. This method has been validated both in conditions of haemodynamic stability in critically ill patients as well as in unstable conditions, such as in liver transplantation [22–25]. Both systems have algorithms which calculate the constant K ('rate constant') using an equation which deals with the elimination phase ('backward dynamic extrapolation') [9]. The ICG kinetic parameters are determined by monoexponential transformation of the original ICG concentration

curve, backward extrapolation to the time point 'zero' (100 %), and describing the decay as percentage change per time [9]. The algorithm was validated by Purcell et al. determining ICG_{R15} with LiMON and direct measurement of blood samples [26]. The most recent revisions on this item insist on the need for haemodynamic stability in order to obtain reliable data on liver function [9, 11]. In fact, as already underlined, hepatic blood flow and cellular uptake are variables able to impact on ICG elimination (increasing or decreasing the elimination). The hepatic blood flow can be altered by systemic factors (reduced cardiac output able to impact on the hepatosplanchnic perfusion) or by local factors (thrombosis of the hepatic artery or abdominal hypertension); both tend to reduce ICG elimination. On the contrary, the possibility exists that a splanchnic hyperperfusion results in a rise in the extraction of ICG and therefore in a (false) increased PDR.

True pathological ICG_{PDR} or ICG_{R15} is present in the case of end-stage liver failure (cirrhosis) or of severe rejection after liver transplantation, both conditions able to reduce ICG liver extracting abilities [9, 10]. Elevated ICG_{R15} in cirrhotic patients may be due to:

1. Decreased ICG transport from the systemic circulation to the liver
2. Decreased uptake from the sinusoids into hepatocytes

Altered ICG_{PDR} and ICG_{R15} are present also in case of cholestasis: as mentioned above, ICG and bilirubin, competing for the same carrier in the transport process in hepatocytes (sodium taurocholate cotransporting peptide), can alter ICG elimination parameters (by competition and not by functional defect). This condition, not uncommon in the early postoperative period of liver transplantation, can be associated with falsely pathological results, leading to misinterpretation of the tests. Generally speaking, the pathological results may be wrongly attributed to a condition of liver dys/malfunction (falsely reduced function) which might not be the real condition: falsely altered ICG_{R15} or ICG_{PDR} is present when serum bilirubin level is >3 mg/dl [9, 10]. Thus, extreme caution must be used interpreting ICG tests in the presence of hyperbilirubinaemia. In the literature, bilirubin level above 3 mg/dl is reported as the cut-off value: in AA's personal experience in a series of liver-transplanted patients, the cut-off should be at 6 mg/dl [27].

ICG_{PDR} and ICG_{R15} can be used as a starting point for preoperative screening and evaluation of the functional reserve in the case of liver resection, as proposed by Makuuchi's group [8]; with sequential assessments during liver transplantation or during the early postoperative period of liver transplant (OLT) (functional recovery of the transplanted liver); after hepatic resection (functional assessment of the remnant liver after hepatic resection, also in case of living-related donation). In both cases, mandatory is caution in interpreting the results in the presence of hyperbilirubinaemia, frequent in post-liver transplantation and able to give false/altered information on ICG results (high R15/low PDR) [27]. Finally, too short intervals between sequential ICG administrations (<30 min) might significantly alter ICG clearance parameters: this phenomenon is correlated with a baseline drift associated with residual circulating ICG, possibly leading to an (incorrectly) increased ICG_{PDR} [9].

Clinical indications for ICG elimination in perioperative liver medicine and ICU are the following [3, 9–11]:

1. Assessment of hepatic functional reserve and prediction of mortality and morbidity in hepatic resection in cirrhotic patients
2. Evaluation of liver function in cadaveric and living donors (not included in this review)
3. Quality assessment of functional recovery of the liver graft in liver transplant (OLT) recipient
4. Prognostic index in critically ill patients with septic shock in the ICU

13.6   ICG Clearance in the Preoperative Assessment of Liver Resection in Cirrhotic Patients

Liver resection and liver transplantation are the surgical procedures able to treat or even cure hepatocellular carcinoma in patients with cirrhosis. Liver resection is reserved to patients with compensated liver function as assessed by static or dynamic tests, scores and imaging [28]. Despite the improvements in surgical techniques and perioperative management, postoperative liver failure still remains an extremely feared complication in cirrhotic patients undergoing liver resection: it ranges, according to the literature, between 5 and 8 % and is associated with a high mortality rate [9, 30–32]. As a matter of fact, while Imamura et al. reported in 2003 0 % mortality out of 1,056 hepatectomies [29], other series still report mortality rate ranging from 2 to 5 % [11, 25–29]. Inadequate functional hepatic reserve, the extent of resection, blood loss/transfusion needs and severe sepsis/septic shock are among the major causes of postoperative liver failure, more frequent in cirrhotic patients [32–38]. Preoperative evaluation of the extent of liver resection is usually based on clinical conditions (the presence or absence of ascites and hepatic encephalopathy), routine liver function tests (AST/ALT, bilirubin, ALK), dedicated MRI/CT volumetric imaging for the estimation/prediction of the volume of the remnant liver and scoring systems [11, 35–38]. For a global assessment, Child–Pugh (CTP) and MELD scores are the most widely used classification systems in clinical practice [32–37]. CTP score was introduced in 1964 by Child and Turcotte and then modified in 1973 by Pugh (CTP) [39, 40] to predict the operative risk in cirrhotic patients undergoing shunt surgery for portal hypertension (Fig. 13.8). Using common biochemical (albumin, bilirubin, prothrombin time) and clinical parameters (the presence of ascites and encephalopathy, classified according to increasing severity), the Child–Pugh classification identifies in chronic liver diseased patients three classes of severity (A, B, C). Different scores for different values of the biochemical and clinical parameters identified subgroups of patients at increasing severity within the three classes (A 5–6, B 7–9; C 10–15) [11]. The classes and the score are able to predict mortality after general surgery in the different classes (CTP A-10 %; CTP B up to 30 %; CTP-C >50 %) [9]. Major flaws of CTP score are global (instead of regional) evaluation of liver function and no indication of the amount of liver parenchyma safely resectable [9, 10] (Fig. 13.6).

Parameters	Child–Pugh scores		
	1 point	2 points	3 points
Albumin (mg/dl)	>3.5	3.5–2.8	<2.8
Bilirubin (mg/dl)	<2	2–3	>3
PT-INR	<1.7	1.7–2.3	>2.3
PT (%)	>70	40–70	<40
Ascites	None	Small or controlled	Tense
Encephalopathy	Absent	State I or II	State III or IV

Class A: 5–6 total points, class B: 7–9 total points, class C: 10–15 total points

Fig. 13.6 Child–Pugh classification (From Mizuguchi et al. [11])

MELD =9.57 × loge(creatinine, mg/dl) + 3.78 × loge (total bilirubin, mg/dl + 11.2 × loge (INR) + 6.43

MELDNa =MELD + 1.59 × x (135 – serum sodium)

iMELD = MELD score + (age × 0.3) – (0.7 × serum sodium) + 100

MESO index = [MELD/Na (mEq/l)] × 100

UKELD = 5 × [1.5 × loge (INR) + 0.3 × loge(creatinine, μmol/l) + 0.6 × loge (bilirubin, μmol/l) – 13 × loge(serum sodium, mmol/l + 70]

Re-weighted MELD = 1.266 loge (1 + creatinine, mg/dl) + 0.939 loge (1 + bilirubin, mg/dl) + 1.658 loge (1 + INR)

MELDNa model for end-stage liver disease with the incorporation of serum, *iMELD* integrated model for end liver disease, *MESO* model for end-stage liver disease to sodium, *UKELD* United Kingdom end-stage liver disease. *INR* international ratio

Fig. 13.7 MELD and derived scores (From Mizuguchi et al. [11])

In spite of that, in the Western world, the liver function is still evaluated primarily using CTP [39, 40] and the degree of portal hypertension: hepatic resection in cirrhotic patients is usually reserved for Class A patients and, with limitations, for class B patients (vide infra). In this specific setting, the definition of the extent of the resection is crucial to avoid postoperative hepatic dysfunction [8, 29–32].

The use of MELD score and its derivates (Fig. 13.7, MELD, NaMELD and iMELD) is instead controversial in this specific setting. The MELD score is based on prothrombin time (PT) as INR, bilirubin and creatinine. MELD was first introduced to evaluate the outcome in patients undergoing transjugular intrahepatic portosystemic shunt (TIPS): now MELD score is widely used to assess the severity of chronic liver diseases and its prognosis, as a prognostic indicator of survival in patients awaiting liver transplantation and to prioritise the transplant procedure [41–43]. Its predictive value for mortality in liver resection is debated, due to the narrow range of values in which it is used. In a retrospective study, Cucchetti et al. observed a high frequency of postoperative liver failure in patients with MELD >10 [44]. While uniform agreement exists to exclude for hepatic resection patients in CTP class C or with MELD score >14, subjects in CTP class B or with MELD score ranging from 9 to 14 should undergo a thorough evaluation to determine if and to what extent a liver resection might be feasible [44–46].

On the contrary, the Eastern surgical schools (Japanese, Chinese and Korean) have used, since the 1980s, the quantitative tests, particularly ICG clearance (usually as ICG $_{R15}$) [8, 34–36] to assess the maximum extent of major hepatic resection associated with good function of the remnant liver. Recently, ICG$_{R15}$ was added to a score of liver functional evaluation derived from the CTP classification (Liver Damage Grading System) (Fig. 13.8) and recommended by the Liver Cancer Study Group of Japan: according to the proponents, it might become a more accurate tool to assess functional hepatic reserve if compared to the original CTP score [11].

| Parameters	Liver damage grades		
	A grade	B grade	C grade
Albumin (mg/dl)	>3.5	3.5–3.0	<3.0
Bilirubin (mg/dl)	<2	2–3	>3
PT (%)	>80	50–80	<50
Ascites	None	Small or controlled	Tense
$ICGR_{15}$ (%)	<15	15–40	>40
If the liver damage final grade meets more than one grade, then the worst grade should be adopted.			

PT prothrombin green time, *INR* international ratio, *$ICGR_{15}$* indocyanine green retention rate at 15 min

Fig. 13.8 Liver damage grading system (From Mizuguchi et al. [11])

At the beginning of the 1990s, Hemming et al. studied liver function with both conventional and ICG kinetic tests in a group of 22 cirrhotic patients undergoing major liver surgery [46]. While conventional liver function tests were not able to predict mortality, the AAs found ICGcl ≤5.2 ml/kg/min strongly associated with mortality. Lau et al. [15], during the period 1989–1993, preoperatively studied 127 candidates for liver resection with aminopyrine breath test, clearance of amino acids and ICGcl measured as ICG_{R15} (normal value 0–8 %, range 3.5–10.6). Unlike the other tests, ICG_{R15} was able to predict in-hospital mortality and specifically to define the ICG_{R15} values above which the test correctly predicted mortality in major (>14 %) and minor (>23 %) liver resections. According to the literature, resection of three or more Couinaud segments is defined as 'major' resection, 'minor' being considered the resection of up to two contiguous or isolated segments (see Fig. 13.1) [9–11]. Of the utmost importance was in authors' view the thorough preoperative liver function assessment and the meticulous and careful surgical technique. In more recent series, which included younger patients with adequate remnant liver volume [35, 47], ICG_{R15} values associated with mortality after major liver resection were slightly higher (17 % vs. 14 %), thus allowing an extension of the indication of major resections to more compromised patients. In addition to their predictive value, ICG clearance tests may allow a reliable assessment of the extent of the resectable liver parenchyma, keeping in mind in particular that the higher the R15, the smaller the amount of resectable parenchyma should be. In the years 1985–1995, Nonami reported in 318 cirrhotic patients undergoing liver resection a reduction in mortality from 11 to 7 %. The extension of liver resection was mainly guided by an ICG_K algorithm: ICG_K and the amount of blood loss were predictive of mortality [36]. Major liver resections are usually performed with ICG_{R15} <15 %; however, in one series, right hepatectomies were performed in patients with ICG_{R15} >10 % and left hepatectomies with ICG_{R15} between 10 and 19 % [9–11, 48–50]. In other experiences, in the presence of an estimated 'sufficient' remnant liver volume, major hepatic resections were successfully performed with a slightly higher ICG_{R15} (15–20 %) [47]. ICG_{R15} became a reference standard after the publication of the results of Makuuchi's group [8]. The authors reported zero mortality in 1,056 hepatectomies performed in the period 1994–2002; particular attention was given to the following three variables: (i) the presence of ascites, (ii) serum bilirubin values and (iii) ranges of ICG_{R15} [8, 29].

Fig. 13.9 Makuuchi
decision tree to select
operative procedure in
patients with impaired liver
function reserve (From
Mizuguchi et al. [11])
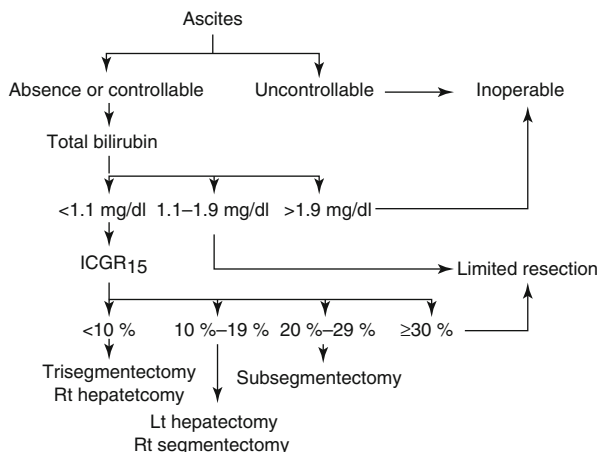
Main points of the algorithm are:

1. Absolute contraindication to hepatic resection in case of uncontrolled ascites and serum bilirubin >1.9 mg/dl
2. Limited (minor) resections possible in case of bilirubin >1 mg <1.9 mg/dl, depending on serum bilirubin
3. With no ascites and serum bilirubin <1.1 mg/dl, different types of liver resection possible according to the interval of ICG $_{R15}$ (see original algorithm in [8] and Fig. 13.9)

Very interesting, even if to be definitively implemented so far, is the use of the test in case of liver resection with ICG_{R15} 15–20 % and remnant liver volume deemed 'not sufficient'. In these cases, preoperative selective portal vein embolisation (PVE) is performed to increase the future 'remnant' liver volume by inducing hyperplasia of liver lobules perfused by the contralateral portal vein [9, 10]. The ICG_{R15} values correlate with volumetric changes of the liver following PVE. ICG_{R15} after embolisation and immediate before surgery correlates with both volumetric and functional reserve changes [9, 51]. The relationship relies upon the preservation of total hepatic blood flow and the induced hepatic hyperplasia (see original algorithm proposed by Poon and Fan) [35]. In 2009, the Japanese guidelines for the treatment of hepatocellular carcinoma recommended ICG_{R15} as test for preoperative liver function evaluation (level of evidence B) [48].

Interesting is the use of ICG kinetic tests (R15 or PDR) during or immediately after surgical resection. Recent studies confirm the ability of the ICG tests to predict postoperative morbidity (mainly hepatic dysfunction), but not mortality, due to the absence of a significant number of deaths [49]. Similar results were found at our centre in a series of 100 consecutive cirrhotic patients undergoing liver resection: ICG $_{R15}$ >40 % was predictive of morbidity but not of mortality [52]. In another smaller study, using intraoperative ICG_{PDR} (normal value >18 %/min), a value of

<9 %/min predicted (sensitivity 88 %, specificity 82 %) postoperative liver failure [49]. In another experience, ICG_{PDR} <7 %/min on the first postoperative day was associated, 2–5 days ahead, with the onset of liver failure [50].

As mentioned above, in case of biliary obstruction, a prolonged preoperative ICG_{R15} value may falsely suggest impaired liver function. Should it be the case, the test must be interpreted with caution and should not be used, as it is, to withhold the intended surgical strategy: in this specific setting, further and multimodal investigations are mandatory [9]. ICG_{R15} remains a valuable tool to assess functional hepatic reserve together with the liver volume evaluation using tomography or magnetic resonance. In the case of hyperbilirubinaemia, as reported by Ge et al., the Korean and Japanese schools suggest Tc-galactosyl serum albumin scintigraphy (Tc GSAS), to study liver function. GSA is the ideal agent to predict hepatocyte mass and function due to the ability to monitor functional status and distribution of asialoglycoprotein receptor [21].

13.7 Indocyanine Green Kinetics and Liver Transplantation

The conventional static tests of liver function may sometimes leave doubts or uncertainties about the functional recovery of the newly grafted liver, both from cadaveric and living donors [9]. The clearance of ICG expressed as plasma disappearance rate (ICG_{PDR}) or K constant of elimination (the use of ICG_{R15}, is, in fact, much less frequent in liver-transplanted patients) has been used to assess liver function in the cadaveric donor before harvesting and in the liver transplant recipient during and after transplantation, to predict early complications and survival of both the graft and the recipient after the transplant procedure [9].

Organ shortage is one of the major problems in the field of organ transplantation. Marginal or so-called extended criteria donors are now increasingly considered for organ harvesting to expand the donor pool. In this setting, ICG_{PDR} was used in few small single centre studies to assess the quality of the potential graft and to assist the decision about using marginal or extended criteria donors. Unfortunately, the role of ICG_{PDR} to assist in the assessment of graft suitability is weak at best: a value < 15 % min^{-1} before organ harvesting was associated with primary graft non-function [9]. A combination of ICG kinetics and MELD score (ICG-MELD score) was recently considered to refine the accuracy of survival prediction in candidates awaiting liver transplantation: the ICG-MELD score improved prediction performance in patients with MELD score ranging from 10 to 30 points (intermediate to severely compromised patients) [53].

In liver-transplanted patients, the most feared complications early after the surgical procedure are primary graft non-function (PGNF) and hepatic artery thrombosis (HAT). Both conditions deserve very aggressive treatment: in large part of the cases, urgent/emergent retransplantation is the only solution able to avoid fatality. The studies of Jalan et al. [54], Plevris et al. [55] and Tsubono et al. [56] at the end of the 1990s confirmed the great interest in the use of ICGcl in assessing early liver function and in predicting graft function, graft and patient survival and the final

outcome. Essentially, in the early post-transplant period, a 'low' ICG_{PDR} (an ill-defined value ranging from 5 to 12 % min^{-1}) was associated with graft malfunction/failure: the major problem in this specific setting is to define a reliable and reproducible cut-off value, not affected by parameters or conditions able to generate falsely altered results (hyperbilirubinaemia, as mentioned above, not uncommon reported early after OLT), which make data unreliable at best and extremely difficult to be interpreted. Jalan et al. [54], invasively studying ICG clearance, observed that ICGcl values greater than 200 ml/min were associated with immediate recovery of liver function and a normal function after 3 months; on the contrary values, <200 ml/min predicted PGNF, retransplantation, long-term care and death. 200 ml/min was found to be the ICG_{cl} value able to predict outcome (100 % sensitivity and 95 % specificity) [55]. Faybik studied the ICGcl in liver-transplanted patients using both invasive (COLD system, Pulsion, Germany) and noninvasive techniques (LiMON, Pulsion, Germany) as ICG_{PDR} [57]. ICG_{PDR} <10 % min was predictive of postoperative complications. In 30 patients who underwent living donor liver transplantation, Hori et al. [58] monitored liver function using ICG test, expressed as ICG_K (DDG-2001 Nihon Kohden) for 14 consecutive postoperative days and then at postoperative days (PODs) 21 and 28. According to the outcome, patients were subsequently allocated to two groups. The six patients with unfavourable outcome (increased morbidity and mortality) had ICG_K <0.180 24 h after transplantation; this value was able to predict poor outcome at 28 days.

More recently, Levesque et al. identified two main objectives: (a) to determine if the value of ICG_{PDR} measured by noninvasive technique (LiMON, Pulsion) might predict early postoperative complications and (b) to hypothesise the cause of early graft dysfunction [59, 60]. The test was performed daily from POD 1 to POD 5. ICG_{PDR} of 24.4±6.8 % was recorded in the group of patients with good functional recovery of the graft, regular postoperative course and favourable outcome [59]. Patients who suffered early complications were retrospectively divided into two groups: the first included patients with early postoperative complications (PGNF, HAT, septic shock or haemorrhagic shock) and the second, patients with late complications (mainly rejection). ICG_{PDR} in the first group was low during the first 5 days (8.8±4.5 %); in the second group, on the contrary, the ICG_{PDR}, initially normal, decreased significantly within 3–5 days (10.3±2.5 %). Levesque et al. proposed an ICG_{PDR} <12.85 % min^{-1} in the very early postoperative days as a marker of almost immediate postoperative complications, mainly associated with hepatocellular dysfunction (PGNF) or perfusion deficit secondary to hepatic artery thrombosis (HAT); late (3–5 days after OLT)-onset low ICG_{PDR} (<12.85 % min^{-1}) was instead associated with acute rejection [60], underlining the importance, in authors' view, of both time course and absolute values of the ICG kinetics. Recently, Olmedilla et al. [61] reported similar results using ICG elimination at the end of surgery (neohepatic phase) or on POD 1. ICG_{PDR} in patients with severe hepatic dysfunction was <10.8 % min and was associated with increased mortality; on the contrary, ICG_{PDR} >10.8 % min was associated with a good outcome and showed high (99 %) negative predictive value [52]. Very recently, Escorsell et al. [62] were not able to confirm the ability of ICG_{PDR} performed on POD 1 to predict liver

dysfunction and survival. In fact, the group of patients with ICG_{PDR} <8.8 % min^{-1} (group A) did not show an outcome worse than the group with value >.8 (group B): in group A, however, bilirubinaemia was significantly higher, likely determining a false reading of the low ICG_{PDR} value (therefore, a falsely malfunctioning graft). Very similar results were found by our group in a series of 76 consecutive patients who underwent OLT. Mazza et al. were unable to confirm ICG_{PDR} <10 % min^{-1} as reliable predictor of both early graft dysfunction and poor outcome; in this experience, ICG_{PDR} <8 % min^{-1} was associated with the presence of serum bilirubin >6 mg/dl (the same was for ICG_{R15}), making the results, as above underlined, unreliable [27]. Essentially, the presence of hyperbilirubinaemia altered the test results, falsely showing an initial hepatic dysfunction that was not confirmed by the subsequent clinical course and outcome of both the graft and the patients. In this study, lactate clearance was strongly correlated with the functional recovery of the grafted livers, showing a high positive predictive value, thus confirming a previous study performed by our group [63]. It has to be underlined that other factors/conditions (different values of total protein or haematocrit) might induce similar interferences with ICG kinetics [64].

The need for caution in the interpretation of low values of ICG_{PDR} in order to indicate malfunction of the graft is having further confirmations in studies using LiMAx test (maximal enzymatic liver function), a test used since 2010 to identify patients at risk for hepatic failure, both after liver surgery or liver transplantation [65, 66, 68]. Intravenously administered ^{13}C-methacetin is metabolised to paracetamol and $^{13}CO_2$. Continuous and noninvasive breath analysis of $^{13}CO_2$ production is measured as a surrogate of maximal liver metabolic capacity. Lock et al. reported a better predictive ability of LiMAx than ICG_{PDR}. Patients suffering from initial graft dysfunction (defined as technical complications or primary non-function ($n=8$)) had significantly decreased LiMAx results, making the test potentially effective to identify very early life-threatening complications after OLT. These observations emphasise once again the importance of the interference of various parameters on PDR/R15 results and the caution needed in the interpretation of these values [9, 10]. In the most recent experience with LiMAx in 167 chronic ESLD patients evaluated for liver transplantation, taking as primary end point 6 months liver-related death, median LiMAx values were significantly lower in patients who died, at variance of ICG_{PDR}, not different in survivors or non-survivors. LiMAx, if compared to ICG_{PDR} and MELD, showed a slightly higher negative predictive value in predicting risk of death within 6 months [66]. The use of ICG kinetics in acute liver failure as prognostic indicator has been reported in small or preliminary series with interesting results [10, 67]: however, it must be underlined that high bilirubin values (present by definition in patients suffering for acute subacute or hyperacute liver failure) might critically influence the results, likely making unreliable or doubtful the tests in this setting. LiMAx has very recently been considered in patients with acute liver failure. The LiMAx was significantly lower in patients who did not recover, whereas neither biochemical parameters nor MELD score showed difference. According to these data, LiMAx test might be effective in predicting the individual prognosis and the need for OLT in ALF [68].

13.8 ICG Kinetics as a Prognostic Score in Intensive Care

ICG kinetics have been long used even within the ICU, to determine the severity of the disease and/or to predict mortality [1, 3, 9, 10, 68–71]. In this setting, it might be interesting to differentiate, having achieved an acceptable haemodynamic stability, the different contributions given to the ICG elimination by parenchymal liver function and hepatic blood flow [1, 68]. In critically ill patients, very common is the use of scores based on clinical and biochemical variables (APACHE II, SAPS II, SOFA), designed to quantify the severity of the disease or to predict mortality. In a retrospective study of 336 critically ill patients, ICG_{PDR} was able to predict mortality in ICU patients similar to SAPS II and APACHE II [70]. Non-survivors had significantly lower values compared with survivors (6.4 %/min vs. 16.5 %/min). In patients with septic shock, ICG kinetics parameters evaluating liver function and perfusion might be able to give a reliable prognostic evaluation. ICG_{PDR} values <8 %/min predicted mortality in patients with septic shock: again sensitivity and specificity were similar to those determined by APACHE II score [70]. Kimura et al. were able to document a favourable outcome associated with an improvement in ICG_{PDR}, while extremely low levels were predictive of poor outcome [71]. It might be hypothesised that in critically ill septic patients in which splanchnic perfusion is appropriately supported by inotropes/pressors, ICG_{PDR} could be considered an indicator of hepatocellular dysfunction if haemodynamic improvement is not associated with a favourable trend in ICG kinetics. Since long, ICG kinetics have been demonstrated of interest to document, in trauma patients, hepatic dysfunction (ICG clearance results preceding the increase in serum bilirubin)[72]. Pollack et al. were able to demonstrate the superiority of ICG clearance compared to the value of bilirubin in predicting survival in patients with trauma or shock [68]. As already reported, the cytokine increase associated with shock might constitute a factor able to interfere with the ICG transport within the liver cell, making not completely reliable the results [9]. Abdominal hypertension (defined as an intraabdominal pressure exceeding 12 mmHg, with values above 20 mmHg associated with abdominal compartment syndrome) [72] might impact on ICG kinetics. Low values of ICG_{PDR} (unfortunately an univocal cut-off is not available, so far) are associated with reduced splanchnic perfusion, and extremely low values of ICG_{PDR} correlate with mortality [9, 10, 72–77]. According to preliminary reports, it might be speculated that low ICG_{PDR}, even if in the presence of normal or near-normal intraabdominal pressure (<15 mmHg) might unveil a suboptimal splanchnic blood flow, thus making ICG_{PDR} a possible early marker of inadequate splanchnic perfusion [76].

Conclusions

Used since the 1960s for research purposes, the ICG kinetics have received a major boost in clinical use in the recent years, with the introduction of reliable and simple noninvasive monitoring methods (LiMON, Nihon Kohden). The applications in the field of major liver surgery (resection in cirrhotic patients) underscore the relevant implications in predicting both the resectability of liver cancer in cirrhotic patients and the potentials for postoperative liver failure:

relevant in this setting are the studies coming from Japan, China and Korea. The ability to predict mortality, however, is still under debate. Despite initial enthusiasms, post-OLT ICG kinetics for the prediction of mortality and morbidity still raise some concerns. This refers, in particular, to the presence of mixed results and 'false positives' in the presence of hyperbilirubinaemia (liver grafts falsely classified, according to ICG_{PDR}, as severely dysfunctioning or at unfavourable outcome). Problems are still encountered with the PDR/R15 cut-off values below which they reliably assess poor graft function. While negative predictive values are indeed relevant in predicting good graft outcome (no complications in the presence of 'normal' PDR or R15 values), caution is still needed in case of 'low' or pathological values. As appropriately commented by Vos et al., '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' [9].

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