Intraoperative ICG plasma disappearance rate helps to predict absence of early postoperative complications after orthotopic liver transplantation

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Abstract

**Background.** Early postoperative complications after orthotopic liver transplantation (OLT) are a common problem in intensive care medicine. Adequate assessment of initial graft function remains difficult, however, plasma disappearance rate of indocyanine green (PDR$_{ICG}$) may have an additional diagnostic and prognostic value in this setting. We retrospectively evaluated the ability of **intraoperative** PDR$_{ICG}$ values to predict absence of early postoperative complications in 62 subjects.

**Methods.** PDR$_{ICG}$ was measured non-invasively by pulse dye densitometry during surgery and was correlated with initial graft function.

**Results.** At the end of surgery, PDR$_{ICG}$ was higher in patients without complications: 24.9 % min$^{-1}$ (n = 40) versus 21.0 % min$^{-1}$, (n=22; p=0.034). An area under the ROC curve (AUROC) for PDR$_{ICG}$ was 0.70, while the AUROC for pH, lactate and PT at ICU admission were 0.53, 0.50 and 0.46, respectively. The AUROC of serum bilirubin and PT at postoperative day 5 were 0.68 and 0.49, respectively. The optimal cut-off PDR$_{ICG}$ value for predicting absence of development early postoperative complications was determined to be 23.5 % min$^{-1}$ with 72.4% sensitivity and 71.0% specificity.

**Conclusions.** Intraoperative point-of-care PDR$_{ICG}$ measurement during OLT already predicts absence of early postoperative complications, better and earlier than clinically used laboratory parameters.
Introduction

Liver transplantation is the treatment of choice for end-stage liver disease, primary hepatic malignancy, irreversible acute liver failure and some metabolic diseases. Nowadays, patient survival rates have been reported to be above 85% after 1 year and 75% after 5 years. The morbidity and mortality after liver transplantation is mainly determined in the early postoperative period because of the occurrence of early postoperative complications such as acute rejection. An accurate and quick recognition of early graft dysfunction is therefore of utmost importance. This may best begin intraoperatively, i.e. at a time when the surgeon is able to decide upon a revision before the patient is transported to the intensive care unit (ICU). Up to now, only postoperative assessment of initial graft function following liver transplantation is performed routinely by a combination of physical examination (e.g. jaundice, initial bile production), laboratory tests (e.g. serum bilirubin, aspartate / alanine aminotransferase (AST/ALT), pH and prothrombine time (PT)) and radiological imaging, e.g. Doppler for assessment of the vascular status of the graft. In spite of using these conventional measurements, assessment of initial graft function accurately is still difficult. Novel point of care monitoring methods using dynamic hepatic function tests have been developed to improve assessment of initial graft function. The determination of the plasma disappearance rate of the dye indocyanine green (PDR$_{ICG}$) has been demonstrated to reflect global liver function reliably. Furthermore, recent studies have demonstrated that determination of the PDR$_{ICG}$ in the postoperative phase is able to predict early, severe complications following liver transplantation. A quick recognition and prediction of absence or presence of early postoperative complications can optimize early postoperative management on the ICU. In case of adequate early graft function, less expensive monitoring during ICU stay might be suitable, while in case of insufficient early graft function the potential for performing early intervention(s) to improve graft function is offered, ideally taking place already in the post-reperfusion stage during transplantation as a quick and direct assessment of graft quality.

We therefore studied whether PDR$_{ICG}$ values, measured already in the intraoperative phase, can predict absence of (developing) early postoperative complications following orthotopic liver transplantation.

Methods

Retrospectively, we studied adult patients undergoing orthotopic liver transplantation (OLT) between August 2006 and February 2010. Grafts from donation after brain death (DBD) and donation after cardiac death (DCD) donors were included. PDR$_{ICG}$ is measured routinely during OLT in our institution (see below). Patients in whom no PDR$_{ICG}$ measurement was performed after graft reperfusion were excluded. The study has been approved by the local medical ethics committee and the requirement for written informed consent was waived (Registration number 20011.150, University Medical Center Groningen, Netherlands).

Anesthetic management:

General anesthesia was standardized and was maintained with isoflurane, sufentanil and vecuronium. Furthermore, patients were ventilated using a volume-controlled mechanical ventilation with a mixture of $O_2$/air ($FiO_2$ 0.30-0.35) and isoflurane.
**Intraoperative PDR\textsubscript{ICG} measurement:**

ICG elimination was measured non-invasively by pulse dye densitometry using either a DDG-2001 monitor (Nihon Kohden, Tokyo, Japan) or a LiMon monitor (Pulsion Medical Systems, Munich, Germany). After bolus administration of 10 mg ICG via a central venous line, an indicator dilution curve is obtained using a finger clip sensor.\textsuperscript{13,14} The ICG disappearance curve is automatically plotted and the downslope of this curve is fitted with a mono-exponential decay function and back-extrapolated to the time of injection by the following equation:

\[ C_{ICG}(t) = C_0 \cdot e^{-k \cdot t}, \]

in which \( C_{ICG} \) represents ICG concentration, \( t \) the time in minutes, \( C_0 \) the extrapolated ICG concentration at \( t=0 \) and \( k \) the elimination constant. PDR\textsubscript{ICG} is calculated from the elimination constant \( k \):

\[ \text{PDR}_{ICG} (\% \text{ min}^{-1}) = k \cdot 100. \]

In our institution, multiple research-based measurements take place at four standardized and well-defined time points, including measurement of the PDR\textsubscript{ICG}.\textsuperscript{15} The following time points are defined:

- **Pre-anhepatic phase:** shortly after induction of anesthesia, before skin incision. This measurement represents the PDR\textsubscript{ICG} of the recipient’s native liver function.
- **Anhepatic phase:** the phase without functional liver. Nevertheless, PDR\textsubscript{ICG} differs from zero in this phase.\textsuperscript{16,17}
- **Post-reperfusion:** 30 minutes after reperfusion of the graft.
- **End of surgery:** during skin closure, after completion of all vascular and biliary anastomoses.

**Study variables:**

Primary endpoint in this study was the absence of early postoperative complications, as defined in table 1. Only early postoperative complications were defined that lead to a therapeutic intervention aimed to prevent graft loss. The accuracy to predict the absence of developing these defined complications of PDR\textsubscript{ICG} measurements were compared with a) the accuracy of measurements frequently used early after surgery (serum PT, lactate and pH at the time of admission to the ICU) and b) the measurements frequently used in the period thereafter (serum bilirubin and serum PT at day 5 after transplantation).

To assess the influence of hemodynamics on PDR\textsubscript{ICG}, we studied the effects of mean arterial pressure (MAP) and dosage of noradrenaline on values of PDR\textsubscript{ICG} after reperfusion and at the end of surgery. In addition, we studied the relationship between the cold ischemia time (CIT) and warm ischemia time (WIT) with PDR\textsubscript{ICG} values. CIT was defined as the time period from in situ flushing of the graft in the donor with cold perfusion solution to removal of the graft from ice before implantation. WIT was defined as the time period between removal of the graft from cold storage and reperfusion of the graft in the recipient. Also, we analysed DBD and DCD donation, the type of vascular anastomosis (piggyback technique and classical anastomosis) and the estimated blood loss. Finally, the relation between the Donor Risk Index (DRI) and the PDR\textsubscript{ICG} was analysed.\textsuperscript{18}
Table 1. Definition of early post-operative complications.

<table>
<thead>
<tr>
<th>Definition</th>
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<tr>
<td>Hepatic artery or portal vein thrombosis, as confirmed by Doppler ultrasonography</td>
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<tr>
<td>Primary graft non-function</td>
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<tr>
<td>Biopsy proven acute rejection (classified according to the Banff grading system) necessitating either an increase in immunosuppressive medication or a steroid bolus</td>
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<tr>
<td>Occurrence of early ischemic biliary lesions within a year after transplantation requiring radiologic intervention(s) or retransplantation</td>
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<tr>
<td>Surgical re-intervention within two weeks after transplantation aimed at maintaining graft viability</td>
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Statistical analysis:
Statistical analysis was performed using SPSS 16.0 (SPSS Inc, Chicago, USA). For continuous data, normal distribution was analysed using the Kolmogorov Smirnov test. If normal distribution was confirmed, the Student’s T test was applied. The Mann-Whitney test was applied for non-normally distributed variables.

For comparison of PDR$_{ICG}$ values between patients with and without early postoperative complications at the 4 time points, with correction for multiple measurements, non-parametrical ANOVA was performed using the Kruskal-Wallis test. The influence of MAP, noradrenaline dosage, CIT, WIT and DRI on post-reperfusion PDR$_{ICG}$ values was analysed using correlation analysis and Pearson correlation coefficients (R) were calculated. Categorical variables were tested using the Fisher’s Exact test. A p-value below 0.05 was considered statistically significant and all tests were two-sided.

To assess the ability of PDR$_{ICG}$ values and conventional laboratory measurements in predicting the absence of early postoperative complications, Receiver Operating Characteristics (ROC) curves were generated and the areas under the ROC curve (AUROC) were calculated. These calculations were performed using the 2 post-reperfusion PDR$_{ICG}$ values and the postoperative serum pH, lactate and PT after admission to the ICU and the serum bilirubin at day 7 after transplantation. An AUROC value above 0.65 was considered clinically relevant.

Optimal cut-off values were determined using the Youden Index, calculated as: sensitivity + specificity -1.

Results

Sixty-two adult patients, who underwent liver transplantation with a full size orthotopic graft, were retrospectively studied. In 94% of these cases a PDR$_{ICG}$ measurement was performed 30 minutes after graft reperfusion while in 90% of the cases a PDR$_{ICG}$ measurement was performed at the end of surgery. The total number of measurements per time point is shown in figure 1. Among the studied patients, 40 patients (65%) did not develop one of the predefined early postoperative complications. The remaining 22 patients developed one or more of the following early postoperative complications: acute rejection (n=11; 3 grade I Banff and 8 grade II Banff cases; 7 patients required an increase in dosage of immunosuppressive medication and 4 patients received a steroid bolus), early ischemic biliary lesions (n=10; median time of diagnosis: 2 months; eventually, 4 patients required retransplantation and 6 patients underwent radiologic intervention) and surgical re-intervention (n=5; either because of revision of the biliary or vascular anastomoses or because of septic peritonitis). None of the patients developed primary non-function, hepatic artery thrombosis, or portal vein thrombosis.
The analysis of patient characteristics showed no differences between patients with and without early postoperative complications with respect to age, gender and MELD score (table 2). Furthermore, there were no differences between primary OLT’s and re-OLT’s with respect to the incidence of early postoperative complications (p=0.24), which was neither found for the type of donor procedure (DBD and DCD, p=0.23). Also the difference in DRI was not significant between the 2 groups: DRI of patients with early postoperative complications was 1.5 (0.9-2.3), compared to 1.4 (0.9-2.7) of patients without early postoperative complications.

<table>
<thead>
<tr>
<th>Gender:</th>
<th>With complications (n = 22)</th>
<th>Without complications (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>12 (20%)</td>
<td>23 (37%)</td>
</tr>
<tr>
<td>Female</td>
<td>10 (16%)</td>
<td>17 (27%)</td>
</tr>
<tr>
<td>Age</td>
<td>52 (25-67)</td>
<td>55 (20-68)</td>
</tr>
<tr>
<td>MELD score</td>
<td>15 (6-38)</td>
<td>13 (6-43)</td>
</tr>
<tr>
<td>Donor Risk Index</td>
<td>1.5 (0.9-2.3)</td>
<td>1.4 (0.9-2.7)</td>
</tr>
<tr>
<td>Sort of OLT:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary OLT</td>
<td>18 (29%)</td>
<td>37 (60%)</td>
</tr>
<tr>
<td>Re-OLT</td>
<td>4 (6%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>OLT indication:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis (viral/auto-immune)</td>
<td>3 (5%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Cryptogenic liver cirrhosis</td>
<td>3 (5%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>PBC / PSC</td>
<td>7 (11%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Alcoholic liver cirrhosis</td>
<td>3 (5%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>0 (0%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (8%)</td>
<td>17 (27%)</td>
</tr>
<tr>
<td>Donor procedure:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donation after brain death</td>
<td>14 (22%)</td>
<td>32 (52%)</td>
</tr>
<tr>
<td>Donation after cardiac death</td>
<td>8 (13%)</td>
<td>8 (13%)</td>
</tr>
<tr>
<td>Vascular anastomosis:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piggyback technique</td>
<td>20 (33%)</td>
<td>38 (61%)</td>
</tr>
<tr>
<td>Classical anastomosis</td>
<td>2 (3%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Estimated blood loss (L)</td>
<td>2.3 (0.7 – 24.4)</td>
<td>2.5 (1.0 – 17.5)</td>
</tr>
<tr>
<td>Cold ischemia time (min)</td>
<td>482 (285 – 701)</td>
<td>445 (153 – 704)</td>
</tr>
<tr>
<td>Warm ischemia time (min)</td>
<td>45 (37 – 77)</td>
<td>44 (30 – 62)</td>
</tr>
</tbody>
</table>

**Table 2:** Demographic data and intraoperative data in patients with and without development of early postoperative complications. Shown are the median value (range) for continuous variables. For categorical variables, the frequency (percentage of total) is given. PBC: Primary Billiary Cirrhosis; PSC: Primary Sclerosing Cholangitis.
Intraoperative $PDR_{ICG}$ pattern:
Starting with a $PDR_{ICG}$ during the pre-anhepatic phase (5.7 (1.6 – 16.0) % min$^{-1}$), $PDR_{ICG}$ decreased significantly during the anhepatic phase to minimal values (2.0 (0.0 – 5.8) % min$^{-1}$), figure 1A. Thirty minutes after reperfusion of the graft, $PDR_{ICG}$ increased significantly (median 22.8 % min$^{-1}$) with a wide range (9.1 – 47.5 % min$^{-1}$). Similar values were found at the end of surgery (23.8 (10 – 42.7) % min$^{-1}$).

Figure 1A. Boxplot of intraoperative $PDR_{ICG}$ values of all patients, n = 62. Shown are the range, 25$^{th}$, 75$^{th}$ percentile and the median.

$PDR_{ICG}$ and absence of early postoperative complications:
There were no significant differences in $PDR_{ICG}$ values between patients without and with postoperative complications at the first 3 intraoperative time points (p = 0.55, p = 0.24, p = 0.12 respectively). However, at the end of surgery, $PDR_{ICG}$ was significantly higher in patients who did not develop early postoperative complications compared to patients who did develop such complications (figure 1B): 24.9 (10.0 – 50.0) % min$^{-1}$ versus 21.0 (12.8 – 42.7) % min$^{-1}$ respectively, p =0.034. A further subgroup analysis between groups of patients with one of the five predefined complications (table 1) revealed no further significant difference in $PDR_{ICG}$ values.

Figure 1B. Boxplot of $PDR_{ICG}$ values at the end of surgery of patients with (grey boxes, n = 22) and without complications (white boxes, n = 40).
Shown are the range, 25$^{th}$, 75$^{th}$ percentile and the median. * P<0.05, Kruskal-Wallis test.
Prediction of the absence of early postoperative complications:
Intraoperatively, the AUROC of the PDR$_{ICG}$ was 0.65 at 30 minutes after graft reperfusion and 0.70 at the end of surgery (p=0.017). In the direct postoperative phase, after admission to the ICU, the AUROC of pH, lactate and PT were 0.53, 0.50 and 0.46 respectively (figure 2A). The AUROC of serum bilirubin at postoperative day 5 was 0.68 (p=0.025), while the AUROC of serum PT at that moment was 0.49 only (figure 2B).
We determined the optimal cut-off PDR$_{ICG}$ value at the end of surgery for prediction of absence of development of early complications at 23.5 % min$^{-1}$, with a sensitivity of 72.4% and specificity of 71.0%.
Accordingly, significantly more patients who did not develop early postoperative complications had a PDR$_{ICG}$ value above this cut-off value, compared to patients with development of those complications at the end of surgery (n = 6 versus n = 16, respectively; p = 0.01).

Figure 2A: ROC-analysis for the prediction of absence of early postoperative complications of the intraoperative PDR$_{ICG}$ values (measured 30 minutes after graft reperfusion and at the end of surgery) and values of the pH, lactate and PT shortly thereafter when the patient was admitted to the ICU. AUROC’s are shown in brackets.
Factors influencing intraoperative $PDR_{ICG}$:
Intraoperative hemodynamic data (MAP and noradrenaline dosage) are given in table 3. Both these variables were not significantly correlated with $PDR_{ICG}$ values.
Furthermore, no significant correlation between length of cold or warm ischemia time and $PDR_{ICG}$ was found 30 minutes after graft reperfusion ($R$ was -0.165 and -0.106, respectively) and at the end of surgery ($R$ was -0.288 and -0.219, respectively).
No differences were found in $PDR_{ICG}$ between patients receiving a DBD graft ($n = 46$) or a DCD graft ($n = 16$). $PDR_{ICG}$ 30 minutes after graft reperfusion was $25.1 \% \text{min}^{-1}$ and $22.5 \% \text{min}^{-1}$, respectively ($p = 0.24$). At the end of surgery, $PDR_{ICG}$ was $25.4 \% \text{min}^{-1}$ and $24.5 \% \text{min}^{-1}$, respectively ($p = 0.74$). The influence of the type of vascular anastomosis could not be further analyzed because in 58 cases a piggyback and only in 4 cases a classical vascular anastomosis was performed. None of the patients required temporary use of a portocaval shunt.
The DRI was not correlated with the $PDR_{ICG}$ measured 30 minutes after graft reperfusion or at the end of surgery ($R = -0.10$ and $R = -0.09$, respectively).

Discussion
In this retrospective study we analyzed intraoperative $PDR_{ICG}$ measurements in 62 adult patients undergoing full size orthotopic liver transplantation. $PDR_{ICG}$ measured in patients at the end of the surgical procedure, was significantly higher in patients who did not develop early postoperative complications. We could define an optimal cut-off value of $PDR_{ICG}$ measured at the end of surgery of $23.5 \% \text{min}^{-1}$ and we found an increased likelihood for absence of early postoperative complications in patients with a $PDR_{ICG}$ value above this cut-off value. In this study, intraoperative $PDR_{ICG}$ values could predict absence of early postoperative complications earlier than clinically used laboratory parameters and this prediction was better than pH, lactate and PT after ICU admission and was
equal to serum bilirubin measured at the 5th postoperative day. These values might be used for an early assessment of graft quality and might offer the potential for performing early interventions to improve graft viability already in the intra-operative phase. We found a typical intraoperative pattern of $PDR_{ICG}$ values: $PDR_{ICG}$ reflects recipient native liver function in the pre-anhepatic phase (figure 1) and in the anhepatic phase, $PDR_{ICG}$ values decrease to almost zero (but not to zero, possibly because of interstitial diffusion of ICG). Subsequently, $PDR_{ICG}$ values increase rapidly after graft reperfusion, depending on adequacy of graft function.

The highest AUROC was found for the $PDR_{ICG}$ value measured at the end of surgery. The AUROC for the $PDR_{ICG}$ value 30 minutes after reperfusion was lower, probably because of the observed wider variation in MAP (see below), creating a wider variation of $PDR_{ICG}$ values. We found however no correlation between either MAP or noradrenaline dosage and $PDR_{ICG}$ values at this time point. Also, at the end of surgery when the surgeons are closing the skin, all anastomoses are already completed. Nevertheless, we found the AUROC to be comparable to that of bilirubin measured at day 5 after transplantation and higher than that of PT at the same day (figure 2B). In addition, the AUROC of $PDR_{ICG}$ was higher than the AUROC’s of pH, PT and lactate measured directly after surgery when the patient was admitted to the ICU. Furthermore, $PDR_{ICG}$ was also more accurate than pH, PT and lactate in this prediction. These conventional liver function tests are in general difficult to interpret and lack sensitivity and specificity for an accurate assessment of initial graft function. Several scoring systems for assessment of initial graft function or occurrence of specific postoperative complications have been suggested and are mostly based on these conventional laboratory measurements in combination with clinical variables such as initial bile production and jaundice. However, a consensus is lacking about the definition of initial graft dysfunction and therefore, we chose absence of clinical diagnoses of early postoperative complications as a primary endpoint in this study instead of using surrogate measures such as serum bilirubin and PT.

The complications listed in table 1 are either caused by a decrease in hepatic blood flow, by global hepatocellular dysfunction, or by a combination of both mechanisms. Hepatic artery or portal vein thrombosis will reduce liver blood flow and are therefore associated with a decrease of the $PDR_{ICG}$. In case of global hepatocellular dysfunction, active sinusoidal uptake of ICG is decreased, resulting in a decrease of $PDR_{ICG}$. Both primary graft non-function and acute cellular rejection are therefore associated with a decreased $PDR_{ICG}$ value. Besides, the occurrence of early ischemic biliary lesions might be caused by a combination of both a reduction in graft (micro-) perfusion and hepatocellular dysfunction.

The finding that, at the end of surgery, still in the intraoperative phase, $PDR_{ICG}$ values could predict the absence of early postoperative complications is in accordance with previous studies that have shown that in the early postoperative phase after OLT on the ICU, early severe complications can be predicted by $PDR_{ICG}$ values, which are also correlated with histopathological liver damage. We determined an optimal $PDR_{ICG}$ cut-off value at the end of surgery of 23.5% min$^{-1}$ for predicting absence of early postoperative. This cut-off value is within the range for the normal population. Others found a much lower cut-off value of 10.8% min$^{-1}$ to predict early postoperative complications. The difference might be explained by the chosen endpoints: the authors chose severe initial graft dysfunction resulting in either death or retransplantation, while we chose a broad group of early postoperative complications. Also, in our study population, none of the patients developed hepatic artery or portal vein thrombosis or had primary graft non-function, conditions that are likely to cause such very low $PDR_{ICG}$ values. If the cut-off value of 10.8% min$^{-1}$ were applied to our data to predict occurrence of early postoperative complications, a very high sensitivity (95%) but a very low
specificity (6%) would have been obtained, implying many false-negative results. The DRI, a scoring system widely used for assessment of graft suitability, is calculated by a combination of donor factors (e.g. age, cause of death, donor height and graft type). Interestingly, we found no correlation between post-reperfusion PDR\textsubscript{ICG} values and DRI. Probably, the observed sample size is too limited to be conclusive in this matter.

In addition, we included both DBD and DCD donors. One might expect lower PDR\textsubscript{ICG} values in the DCD group because of more ischemic damage to hepatocytes. However, we found neither differences in PDR\textsubscript{ICG} values nor differences in complication rate between both groups. The latter is in good accordance to results of other institutions in our country.\cite{1}

**Study limitations:**
At first, the gold standard for determination of liver function with ICG is the ex-vivo measurement of sequential ICG blood concentrations and calculation of ICG clearance, which is a complex and time-consuming method and not suitable for clinical practice.\cite{7}

Alternatively, determination of the PDR\textsubscript{ICG} which is the clinical standard and was used in the current study, does not require measurement of absolute ICG concentrations but measures relative changes in ICG concentration over time.\cite{7,35,36} PDR\textsubscript{ICG} measurements correlate well with ICG clearance calculated from ICG blood concentrations and have been shown to reliably assess global liver function.\cite{7,35,38} In addition, the administered bolus of 10 mg ICG has been shown to enable accurate pulse dye densitometry readings.\cite{39}

At second, a limitation of liver function monitoring using measurement of the PDR\textsubscript{ICG} is the blood flow dependency of this method.\cite{40,41} Due to the high ICG extraction ratio of the liver, clearance of ICG is highly dependent on liver perfusion and thus, the PDR\textsubscript{ICG} value is influenced by changes in cardiac output.\cite{7,42} To assess initial graft function intraoperatively, PDR\textsubscript{ICG} is most ideally measured directly after graft reperfusion. At that moment, one might expect a relatively higher PDR\textsubscript{ICG} value because of reactive hepatic hyperperfusion. Also, this period is sometimes characterized by significant hemodynamic disturbances, reducing the reliability of the PDR\textsubscript{ICG} value when measured directly after graft reperfusion. We did not find a correlation between post-reperfusion PDR\textsubscript{ICG} values and MAP, nor did we find a correlation between PDR\textsubscript{ICG} values and dosage(s) of noradrenaline during those post-reperfusion time points. In addition, the PDR\textsubscript{ICG} value might be overestimated directly after graft reperfusion due to remnant ICG from previous measurements, which can be seen by a drift of ICG baseline concentration and subsequently no measurement can be performed. To exclude influence of hemodynamic instability or remnant ICG, PDR\textsubscript{ICG} was measured 30 minutes after graft reperfusion.

At third, hyperbilirubinemia (> 51 µmol L\textsuperscript{-1}) can reduce PDR\textsubscript{ICG} because ICG and bilirubin are most probably transported by the same carrier.\cite{29}

In conclusion, intraoperative point of care monitoring of liver function by measurement of the PDR\textsubscript{ICG} in patients undergoing liver transplantation is a simple, non-invasive and inexpensive tool that can help to predict absence of early postoperative complications already in the intraoperative phase before the patient is transported to the ICU. Measurement of PDR\textsubscript{ICG} provides an ability to predict absence of postoperative complications in a much earlier phase than postoperatively determined and clinically used laboratory measurements, is even more accurate than prediction by pH, lactate and PT after ICU admission and is comparable with serum bilirubin measured at the 5\textsuperscript{th} postoperative day. Intraoperative PDR\textsubscript{ICG} measurement can therefore be used to reassure adequacy of initial graft function in case of a PDR\textsubscript{ICG} value above 23.5 % min\textsuperscript{-1}, while in case of a PDR\textsubscript{ICG} below this cut-off value,
it can function as an ‘early warning tool’ even intraoperatively for detection of liver graft function and quality which gives the opportunity for interventions to prevent the development of early postoperative complications. In case $PDR_{\text{ICG}}$ is low in the post-reperfusion phase of transplantation while anesthetic management is optimized, direct interventions for correction of (possible) graft compromising circumstances could be performed such as repositioning of the graft or surgical revision of vascular anastomosis. All these interventions could be performed while the patient is still in the OR and are ultimately aimed to prevent graft loss. Furthermore, clinical routing of the postoperative patient might be optimized, based on an early assessment of $PDR_{\text{ICG}}$ and the likelihood of complications.
References


