Prognostic Value of the Indocyanine Green Plasma Disappearance Rate in Critically Ill Patients*

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Objective: Measurement of the indocyanine green plasma disappearance rate (ICG-PDR) has been proposed as a clinical tool for the assessment of liver perfusion and function in transplant donors as well as a prognostic marker. In this study, we analyzed the prognostic value of the ICG-PDR in critically ill patients.

Design: Retrospective analysis.

Setting: Operative ICU of a university hospital.

Measurements and results: We analyzed 336 critically ill patients (120 female and 216 male; age range, 10 to 89 years; mean ± SD age, 53 ± 19 years) who were treated in our ICU between 1996 and 2000. All these patients were hemodynamically monitored by the transpulmonary double indicator (thermo-dye) dilution technique. Each patient received a femoral artery sheath through which a 4F flexible catheter with an integrated thermistor and fiberoptic was advanced into the abdominal aorta. The ICG-PDR was calculated using a computer system. For each measurement, 15 to 17 mL of 2% indocyanine green were injected in a central vein. Statistical analysis using the lowest value of the ICG-PDR in each individual showed that it was significantly lower in nonsurvivors (n = 168) than in survivors (n = 168) [median, 6.4%/min vs 16.5%/min; p < 0.001]. Sensitivity and specificity with respect to survival was analyzed by receiver operating characteristics. The area under the curve (AUC) as a measure of accuracy was 0.815 when using lowest the ICG-PDR in each patient. For ICU admission (data from 178 patients), AUCs were 0.680 for the APACHE (acute physiology and chronic health evaluation) II, 0.755 for the simplified acute physiology score (SAPS) II, and 0.745 for the ICG-PDR.

Conclusion: The ICG-PDR as a marker of liver perfusion and function is a good predictor of survival in critically ill patients: mortality increased with lower ICG-PDR values, and nonsurvivors had significantly lower ICG-PDR values than survivors. Sensitivity and specificity of the ICG-PDR on ICU admission with respect to survival was comparable to that of APACHE II and SAPS II scores.

M ultiple organ failure still remains the most frequent cause of death in intensive care. Thus monitoring of regional organ blood flow and function is often crucial for guiding therapy in critically ill patients and is highly recommended. Although various techniques have been suggested for the estimation of regional perfusion and oxygenation, especially for the liver, methodologic limitations and expensive equipment make only few of them applicable for clinical applications. Currently, liver function is still most widely assessed by serum bilirubin levels. More recently, alternative measures such as the indocyanine green plasma disappearance rate (ICG-PDR) have been suggested. After injection into the circulation, indocyanine green (ICG) is nearly completely eliminated unchanged by the liver into the bile without enterohepatic recirculation. In principle, elimination of ICG from the blood into the bile is determined by several factors: hepatic blood flow, cellular uptake, and excretion. Due to its physical properties, ICG concentration is quantified most

Key words: indocyanine green; liver function; mortality; multiple organ failure; sepsis

Abbreviations: APACHE = acute physiology and chronic health evaluation; AUC = area under the curve; ICG = indocyanine green; ICG-PDR = indocyanine green plasma disappearance rate; ROC = receiver operating characteristic; SAPS = simplified acute physiology score

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commonly photometrically at the absorption maximum of 805 nm. However, since serial blood sampling for extracorporeal ICG concentration analysis is expensive and time-consuming, bedside assessment of the ICG-PDR has become available by a fiberoptic-catheter based technique.\(^6,7\) The ICG-PDR values obtained by this system were found to agree well with values derived from reference arterial blood samples and extracorporeal photometric analysis.\(^8,9\) In this study, we analyzed the prognostic value of the ICG-PDR in a large number of critically ill surgical patients.

**Materials and Methods**

We retrospectively analyzed data from 336 critically ill patients (120 female and 216 male; age range, 10 to 89 years; mean ± SD age, 53 ± 19 years) who were treated in our ICU between 1996 and 2000. Admission diagnosis was sepsis/septic shock according to the criteria of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference\(^10\) (n = 166), ARDS (n = 43), severe head trauma (n = 45), hemorrhagic shock (n = 28), and intracranial hemorrhage (n = 54). Severity of disease on ICU admission was described by an averaged simplified acute physiology score (SAPS) II of 70 ± 17 and an APACHE (acute physiology and chronic health evaluation) II score of 30 ± 6.\(^11,12\) Overall, the mean sepsis-related organ failure assessment score\(^4\) was 14 ± 2. All patients were sedated, intubated, and placed on mechanical ventilation. The patients underwent extended hemodynamic monitoring by the transpulmonary double indicator (thermo-dye) dilution technique when at least one of the following criteria of organ dysfunction was fulfilled: norepinephrine at > 0.1 \(\mu\)g/kg/min; oliguria < 0.5 mL/kg/h for 2 h; \(P_{aO_2}/f\)raction of inspired oxygen < 200 mm Hg; and serum bilirubin level > 34 \(\mu\)mol/L.

Each patient received a 4F flexible aortic catheter with an integrated thermistor and fiberoptic (Pulsocath 4F, PV 2024 L; Pulson Medical Systems; Münich, Germany) that was advanced from a femoral artery sheath. For each injection, 15 to 17 mL of a cooled solution of ICG (Pulsion Medical Systems) dissolved in glucose 5% in a concentration of 2 mg/mL were used for central venous injection (triplex-lumen central venous catheter, Certofix Trio; Braun; Melsungen, Germany). For triplicate measurement of cardiac output, the ICG injection was followed by two bolus injections of cooled saline solution. ICG-PDR was calculated using a computer system (COLD-Z021; Pulson Medical Systems).\(^6\) In principle, the ICG-PDR is determined by monoeponential transformation of the original ICG concentration curve, backward extrapolation to the time point “zero” (100%), and describing the decay as percentage change per time. Measurements of ICG-PDR were mandatory at least twice per day, since our ICU is managed in a two-shift system.

In general, ICG-PDR monitoring was used to optimize regional perfusion and function. Since the transpulmonary double-indicator dilution technique simultaneously allows assessment of cardiac output and myocardial preload by intrathoracic blood volume, strategies to improve hepatic blood flow and oxygenation included optimized fluid status, inotropics (dobutamine), and vasopressors (norepinephrine) to keep mean arterial pressure > 70 mm Hg.

**Statistical Analysis**

Statistical analysis for the ICG-PDR in survivors (n = 168) and nonsurvivors (n = 168) was based on the lowest value of the ICG-PDR in each individual. All values are given as mean ± SD and median. Box plot descriptive statistics, Mann-Whitney U test, and \(x^2\) tests with Yates correction were made using statistical software (SPSS for Windows version 9.0, SPSS; Chicago, IL). For the determination of receiver operating characteristic (ROC) curves and comparison between different ROC curves, we used ROC curve analysis software (MedCalc Version 4.16e-Windows 3.1; Mariakerke, Belgium). Statistical significance was considered at \(p < 0.05\).

In principle, ROC statistics allow plotting the true-positive rate against the false-positive rate for the different possible cut points of a diagnostic test. ROC curves demonstrate the tradeoff between sensitivity and specificity. In general, the closer the curve follows the left-hand border and then the top border of the ROC space, the more accurate the test. *Vice versa*, the closer the curve comes to the 45° diagonal of the ROC space, the less accurate the test. The area under the curve (AUC) is a measure of accuracy, the higher the AUC the higher the accuracy of the test. ROC statistics are commonly used to assess the sensitivity and specificity of a test with respect to variables such as survival.

**Results**

Demographic data and patients’ characteristics are summarized in Table 1. In our results, the ICG-PDR was significantly lower in nonsurvivors than in survivors (mean, 8.0 ± 6.7%/min; median, 6.4%/min; vs mean, 16.7 ± 7.6%/min; median, 16.5%/min, respectively \([p < 0.001]\); Fig 1). Patients with sepsis (n = 166) had a significantly lower ICG-PDR than those without sepsis (n = 170); median, 6.9%/min vs 16.1%/min, respectively \([p < 0.001]\). By separating several ranges of lowest ICG-PDRs, the analysis indicates significantly increasing mortality with a lower ICG-PDR. In detail, mortality was approximately 80% in patients with ICG-PDRs < 8%/min, and survival was approximately 80% in patients with ICG-PDRs > 16%/min (Fig 2). The analysis of three different subgroups of patients (sepsis, ARDS, and all others) showed that within these groups, survivors had significantly higher ICG-PDR than nonsurvivors. In detail, mean ICG-PDR was 5.4%/min vs 14.0%/min for the subgroup sepsis, 8.1%/min vs 14.7%/min for the ARDS subgroup, and 11.9%/min vs 18.8%/min for the “all others” subgroup (Fig 3).

ROC statistics using the lowest ICG-PDR value in each individual revealed an AUC of 0.815 with a cutoff point of ≤ 10.5%/min (Fig 4). In 178 of the 336 patients (53%), the first ICG-PDR measurement was made within 24 h after admission to the ICU. Since scores of severity of illness are only validated for the first 24 h after ICU admission, we compared APACHE II, SAPS II, and ICG-PDR on ICU admission by ROC statistics. AUCs were 0.680 for APACHE II, 0.755 for SAPS II, and 0.745 for ICG-PDR (Fig 5). Only the comparison between AUCs for APACHE II and SAPS II showed a statistically significant difference \((p = 0.05)\).
The mean time elapsed between ICU admission and the lowest ICG-PDR value was 7.6 days. In this large sample of critically ill patients undergoing femoral artery cannulation, we observed only four patients who required surgical intervention due to occlusion of the vessel, peripheral embolization, or bleeding complications. No allergic reactions (which have been reported to occur with an incidence of 1:40,000)\textsuperscript{13} were observed.

### Discussion

There is evidence from several previous studies\textsuperscript{14–17} that have analyzed a small number of patients with specific disorders that the ICG-PDR can be used as a prognostic tool. Previous studies have not used a fiberoptic system that enables measurement of the ICG-PDR at the bedside. We therefore tried to assess the value of the ICG-PDR in a wider variety of critically ill patients. In our study, the ICG-PDR as a marker of liver perfusion and function was found to be a good predictor of survival in critically ill patients: mortality increased with lower ICG-PDR values, and nonsurvivors had significantly lower ICG-PDR values than survivors. Patients with sepsis had significantly lower ICG-PDR values than nonseptic patients. The analysis on subpopulations of patients showed that in either sepsis, ARDS, and all other patients, the ICG-PDR was always significantly higher in survivors. This finding indicates that the

<table>
<thead>
<tr>
<th>Variables</th>
<th>Survivors (n = 168)</th>
<th>Nonsurvivors (n = 168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male gender, No.</td>
<td>61/107</td>
<td>51/109</td>
</tr>
<tr>
<td>Age</td>
<td>10–89 (47 ± 19) 48</td>
<td>10–89 (59 ± 18) 62\textsuperscript{†}</td>
</tr>
<tr>
<td>SAPS II</td>
<td>35–108 (63 ± 13) 61</td>
<td>30–116 (75 ± 17) 73\textsuperscript{†}</td>
</tr>
<tr>
<td>APACHE II</td>
<td>13–41 (28 ± 5) 28</td>
<td>14–48 (31 ± 7) 30\textsuperscript{†}</td>
</tr>
<tr>
<td>SOFA</td>
<td>5–20 (12 ± 3) 12</td>
<td>5–21 (14 ± 3) 14\textsuperscript{†}</td>
</tr>
<tr>
<td>Sepsis, No.</td>
<td>51</td>
<td>115</td>
</tr>
<tr>
<td>ARDS, No.</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td>Severe head trauma, No.</td>
<td>35</td>
<td>10</td>
</tr>
<tr>
<td>Intracranial hemorrhage, No.</td>
<td>39</td>
<td>15</td>
</tr>
<tr>
<td>Hemorrhagic shock, No.</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Extended monitoring, d</td>
<td>1–34 (7 ± 5) 5</td>
<td>1–49 (9 ± 8) 7\textsuperscript{†}</td>
</tr>
<tr>
<td>ICU stay, d</td>
<td>1–121 (24 ± 17) 20</td>
<td>0–126 (18 ± 21) 11\textsuperscript{†}</td>
</tr>
</tbody>
</table>

*Data are presented as range (mean ± SD) median unless otherwise indicated. SOFA = sepsis-related organ failure assessment. \textsuperscript{†}Significantly different between both groups (p < 0.0001); Mann-Whitney U test. \textsuperscript{‡}Significantly different between both groups (p = 0.01).

The mean time elapsed between ICU admission and the lowest ICG-PDR value was 7.6 days. In this large sample of critically ill patients undergoing femoral artery cannulation, we observed only four patients who required surgical intervention due to occlusion of the vessel, peripheral embolization, or bleeding complications. No allergic reactions (which have been reported to occur with an incidence of 1:40,000)\textsuperscript{13} were observed.

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![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21984/ on 06/22/2017)

**Figure 1.** Box plot for survivors and nonsurvivors. Bold lines indicate medians, box plots indicate 25th to 75th percentiles, and bars indicate the 1.5-fold of the whole box length. Circles indicate values between 1.5-fold to threefold of the whole box length, and outliers (outside threefold of the whole box length) are indicated by asterisks. The bold asterisk indicates statistical significance (Mann-Whitney U test).

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21984/ on 06/22/2017)

**Figure 2.** Mortality as a function of ICG-PDR. Patients were classified into four groups according to their lowest ICG-PDR value. The asterisk indicates statistical significance to the next higher ICG-PDR group (χ² test).
ICG-PDR is a reliable prognostic marker independently from the underlying disease. Furthermore, the ICG-PDR on ICU admission as one single variable was found to be as accurate as more complex scores (i.e., APACHE II and SAPS II) with respect to outcome prediction. Noteworthy, ROC statistics with respect to survival revealed a higher AUC for the ICG-PDR when using the lowest value in each patient.

As early as 1960, Wiegand et al 18 showed that ICG, a substance that is nearly completely eliminated unchanged by the liver into the bile,18–21 had a significantly shorter half-life in normal healthy control subjects when compared to patients with a preexisting liver disease. Normal values for ICG clearance and the ICG-PDR are considered to be \( > 700 \text{ mL/min/m}^2 \) and \( 18\%/\text{min} \), respectively.22

The clinical value of the ICG-PDR has already been demonstrated for evaluation of donor organs for transplantation. In 41 cases, successful transplantation was found to be correlated to organ function: organs with a poor function as indicated by ICG-PDR values were associated with higher rates of discarded grafts. A borderline value for an ICG-PDR of \( 15\%/\text{min} \) was identified as suitable for transplantation.3 Hoeft\(^7\) analyzed nine patients undergoing liver transplantation and described the measurement of ICG clearance to reflect organ function well with low preoperative values, signs of reactive hyperemia in the postanhepatic period, and then return to nearly normal values for the next 24 h. Oellerich et al\(^4\) evaluated different variables of liver function in potential candidates for hepatic transplantation in 107 adult and 57 pediatric patients. In the survival analysis, ICG half-life was ascribed to be the best predictor of prognosis in adult and pediatric patients but also within the different groups of liver cirrhosis. All other parameters, such as serum bilirubin levels, albumin and cholinesterase, or the Child-Pugh score, were found to be inappropriate in assessing short-term prognosis in cirrhosis independent from the etiology of the underlying liver disease.

Hemming et al\(^5\) reported ICG clearance to be a good predictor of successful hepatic resection in cirrhotic patients. Patients with higher values had a significantly lower 30-day mortality. No other liver function test was useful in determining outcome of resection, and an ICG clearance of 5.2 mL/min/kg was identified as cutoff point at which hepatic resection should not be attempted.

Gottlieb et al\(^23\) studied seven patients and reported that the ICG-PDR is an early indicator of

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**Figure 3.** Box plot for the different subgroups of patients (sepsis, ARDS and all others). Bold lines indicate medians, box plots indicate 25th to 75th percentiles, and bars indicate the 1.5-fold of the whole box length. Circles indicate values between 1.5-fold to threefold of the whole box length, and outliers (outside threefold of the whole box length) are indicated by asterisks. The bold asterisk indicates statistical significance (Mann-Whitney U test).

**Figure 4.** Sensitivity and specificity of lowest ICG-PDR with respect to outcome according to ROCs in 336 patients. The AUC was 0.815.
hepatic dysfunction following injury. The ICG-PDR was found to precede an increase in serum bilirubin levels, and therefore to be more sensitive in the assessment of developing organ dysfunction. In patients with trauma or shock, Pollack et al. demonstrated that the ICG-PDR discriminated survivors from nonsurvivors (15.0 ± 6.9%/min vs 6.6 ± 5.0%/min, p < 0.0005) while serum bilirubin levels failed to differentiate between the two groups of patients. In 131 critically ill patients, Ritz et al. found that ICG half-life was highest in patients with preexisting liver disease and circulatory shock. ICG half-life time was found to have a practical value not only for rapid identification of hepatic insufficiency but also for objective measurement of perfusion deficit.

Furthermore, the ICG-PDR has been demonstrated to be a prognostic marker in critically ill patients. By analyzing 98 data sets from 39 critically ill surgical patients, of whom 5 died, survivors had significantly higher ICG-PDR values, with a mean value of 11.1 ± 7.1%/min vs. 4.8 ± 4.3%/min, respectively. In our large study population, we used the lowest ICG-PDR in each patient, and the mean ICG-PDR was 16.7 ± 7.6%/min in survivors and 8.0 ± 6.7%/min in nonsurvivors.

In a previous analysis, we showed in 25 critically ill patients, of whom 14 died, that serum bilirubin levels failed to differentiate between survivors or nonsurvivors at any time point of the 4 days before discharge or death. However, the ICG-PDR was significantly higher (mean, 22%/min vs 11%/min, respectively) in survivors at the last 2 days prior to discharge or death.

Although the technology was developed several years ago, a new transcutaneous pulse densitometry device that is less invasive and simple to apply has just recently been put to use in the clinic. We previously reported the agreement between invasive arterial (fiberoptic-based) and transcutaneous (pulse densitometry) assessment of the ICG-PDR in critically ill patients receiving mechanical ventilation while receiving vasoactive drugs; noninvasive assessment was found to be a reliable alternative.

In conclusion, the ICG-PDR was found to be a good predictor of survival in critically ill patients. For the future, measurement of the ICG-PDR seems to be a promising clinical tool, particularly since accurate and less invasive transcutaneous assessment has become possible.

REFERENCES


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