

# Effects of intra-abdominal pressure on liver function assessed with the LiMON in critically ill patients

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**Background:** Intra-abdominal pressure (IAP) and intra-abdominal hypertension (IAH) are associated with significant morbidity and mortality in critically ill patients. Our aim was to assess the effects of IAH on liver function using the noninvasive liver function monitoring system LiMON and to assess the prognostic value of IAP in critically ill patients.

**Methods:** We conducted a retrospective analysis of critically ill patients who were treated in the intensive care unit (ICU). The IAP and indocyanine green plasma disappearance rate (ICG-PDR) measurements were made within 24 hours after admission to the ICU and repeated 12 hours later. Intra-abdominal pressure was measured via a Foley bladder catheter, and ICG elimination tests were conducted concurrently using the LiMON.

**Results:** We included 30 critically ill patients (17 women and 13 men aged 28–89 yr) in our analysis. Statistical analysis showed that the baseline IAP values were significantly higher among nonsurvivors than survivors (19.38 [standard deviation; SD 2.08] v. 13.07 [SD 0.99]). The twelfth-hour IAP values were higher than baseline measurements among nonsurvivors (21.50 [SD 1.96]) and lower than baseline measurements among survivors (11.71 [SD 1.54]); the difference between groups was significant ( $p < 0.001$ ). The baseline ICG-PDR values were significantly lower among nonsurvivors than survivors (10.86 [SD 3.35] v. 24.51 [SD 6.78]), and the twelfth-hour ICG-PDR values were decreased in all groups; the difference between groups was significant ( $p < 0.001$ ).

**Conclusion:** Our results suggest that measurement of ICG-PDR with the LiMON is a good predictor of the effects of IAP on liver function and, thus, can be recommended for the evaluation of critically ill patients.

**Contexte :** L'élévation de la pression intra-abdominale (PIA) et l'hypertension intra-abdominale sont associées à des taux importants de morbidité et de mortalité chez les patients en état critique. Nous voulions évaluer les effets de l'hypertension intra-abdominale sur la fonction hépatique en utilisant le système de surveillance non effractif de la fonction lymphatique LiMON et évaluer la valeur de la PIA comme pronostic chez des patients en état critique.

**Méthodes :** Nous avons procédé à une analyse rétrospective des dossiers de patients en état critique traités aux soins intensifs. Les mesures de la PIA et du taux de disparition plasmatique du vert d'indocyanine (TDP-VIC) ont été effectuées dans les 24 heures suivant l'admission aux soins intensifs et répétées 12 heures plus tard. On a mesuré l'élévation de la pression intra-abdominale au moyen d'une sonde vésicale de Foley et on a effectué des mesures du TDP-VIC simultanément au moyen du système LiMON.

**Résultats :** Notre analyse a porté sur 30 patients en état critique (17 femmes et 13 hommes âgés de 28 à 89 ans). L'analyse statistique a démontré que les valeurs de référence de la PIA étaient beaucoup plus élevées chez les non survivants que chez les survivants (19,38 [écart-type; ET 2,08] c. 13,07 [ET 0,99]). Les valeurs de la PIA à 12 heures étaient plus élevées que les mesures de référence chez les non survivants (21,50 [ET 1,96]) et moins élevées que les mesures de référence chez les survivants (11,71 [ET 1,54]). La différence entre les groupes était significative ( $p < 0,001$ ). Les valeurs de référence du TDP-VIC étaient beaucoup moins élevées chez les non survivants que chez les survivants (10,86 [ET 3,35] c. 24,51 [ET 6,78]) et les valeurs du TDP-VIC à 12 heures avaient diminué dans tous les groupes. La différence entre les groupes était significative ( $p < 0,001$ ).

**Conclusion :** Nos résultats indiquent que la mesure du TDP-VIC au moyen du système LiMON constitue un bon prédicteur des effets de la PIA sur la fonction hépatique et qu'il est donc possible de la recommander pour évaluer des patients en état critique.

Intra-abdominal pressure (IAP) is the steady-state pressure concealed within the abdominal cavity and is influenced by body weight, body position and abdominal muscle activity.<sup>1-3</sup> A transient increase in IAP, such as pneumoperitoneum during laparoscopic surgery, causes only minimal adverse effects. Several clinical conditions, such as ascites and blood accumulation, tumours, burn eschars, edema, bowel distension<sup>5</sup> and closure of a swollen and noncompliant abdominal wall,<sup>6</sup> can cause a persistent increase in IAP.<sup>4-8</sup>

There has been a growing interest in the concept of IAP and in the impact of intra-abdominal hypertension (IAH) on organ dysfunction in critically ill patients.<sup>8,9</sup> A pathologic increase in IAP has negative effects on splanchnic, respiratory, cardiovascular, renal and neurologic function. Intra-abdominal hypertension is defined by a sustained or pathologic elevation in IAP equal to or above 12 mm Hg, whereas abdominal compartment syndrome (ACS) is defined as an IAP above 20 mm Hg. Intra-abdominal hypertension not only has harmful consequences for different organ systems, but also is associated with mortality.<sup>8-12</sup> In addition, it is associated with splanchnic hypoperfusion; thus, monitoring of regional organ blood flow and function is often crucial for guiding therapy in critically ill patients and is highly recommended.<sup>10,11,13</sup>

The dynamic liver test indocyanine green plasma disappearance rate (ICG-PDR) should provide better direct measurement of liver function and has been suggested as a marker of global hepato-splanchnic blood flow.<sup>14</sup> The ICG-PDR is the most commonly used ICG-derived parameter for clinical and experimental assessment of liver function; the normal range is 18%–25% per minute. Noninvasive means of measuring ICG elimination using dye densitometry have been described since 1967, and the advent of pulse oximetry and subsequently pulse dye densitometry have led to the development of commercially available equipment for pulse spectrophotometry.<sup>15</sup> The only such device currently in use in Turkey is the noninvasive liver function monitoring system LiMON (Pulsion Medical Systems). Previous studies have shown the value of measuring ICG-PDR for assessing prognosis.<sup>16,17</sup> The aim of this study was to assess the effects of IAH on liver function using the LiMON and to assess the prognostic value of IAP in critically ill patients.

## METHODS

The Regional Committee on Medical Research Ethics approved this study. We retrospectively enrolled all new, consecutive patients admitted to the general and surgical

intensive care unit (ICU) for more than 24 hours in a 1-year period (Jan. 1 to Dec. 30, 2008). Inclusion was contingent on the following clinical factors, previously defined by Malbrain and colleagues:<sup>8</sup>

- abdominal surgery (with or without laparoscopy, reduction of hernia, tight closure, or abdominal banding with postoperative Velcro belt to prevent incisional hernia);
- hemoperitoneum caused by either intra- or retroperitoneal bleeding;
- abdominal infection (e.g., pancreatitis, peritonitis, abscess); and
- ileus, whether paralytic, mechanical or pseudo-obstructive, defined as abdominal distention, absence of bowel sounds, failure of enteral feeding evidenced by gastric dilation or gastroparesis with a gastric residual greater than 1000 mL.

In addition to these clinical concomitant factors, patients who had an IAP greater than 12 mm Hg within 24 hours after admission to the ICU and who had documented baseline and repeated twelfth-hour IAP and ICG-PDR measurements were selected and enrolled into the study.

Our ICU included 17 beds, and the physicians had to have experience measuring IAP. Exclusion criteria were possible or confirmed pregnancy and presence of 1 or more of the following: hemodynamic instability (defined as a systolic blood pressure < 100 mm Hg), heart failure (class III or IV of the New York Heart Association), renal failure (RIFLE classification),<sup>18</sup> known or suspected brain death, pelvic fracture, hematuria and neurogenic bladder.<sup>19</sup>

We recorded age, sex, clinical and surgical status, diagnoses, Acute Physiology and Health Evaluation (APACHE II) and Sepsis-related Organ Failure Assessment (SOFA) scores on admission, baseline and twelfth-hour IAP, ICG-PDR, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities for each patient. We also recorded their length of stay in the ICU and survival. Patients were followed until death or discharge from the ICU.

Patients received mechanical ventilation with oxygen-enriched air to attain acceptable blood gases, and extubation was undertaken when indicated clinically. Extubation was performed only when there was no evidence of bleeding and when the patient was alert, cardiovascularly stable, normothermic and had an arterial oxygen tension greater than 10 kPa on an inspired oxygen concentration lower than 40% and a positive end expiratory pressure less than 5 cm H<sub>2</sub>O.<sup>20</sup>

All patients received adequate initial resuscitation, and daily fluid balance was calculated. A 14- to 16-French gauge Levin nasogastric feeding tube (Pharma-Plast) had

been inserted into each patient's stomach as part of clinical care, and the correct gastric position of the feeding tube was confirmed by radiology.<sup>21</sup> In addition to broad-spectrum antibiotic therapy, the source of infection was eradicated whenever possible. All patients had arterial catheters and central venous catheters via the subclavian approach. Mechanical ventilation occurred in volume- or pressure-controlled modes during continuous sedation with midazolam and fentanyl.<sup>22</sup>

Vasopressors were administered to maintain the mean arterial pressure at levels greater than 65–70 mm Hg. The vasopressor agents and corresponding dose ranges were norepinephrine (3–40 µg per min), epinephrine (2–100 µg per min) or dopamine (6–30 µg/kg per min). The need for red blood cell transfusion was determined by each patient's physician.<sup>23</sup>

### Technique of IAP measurement

We used the revised closed system repeated-measurement technique for measurement of bladder pressure.<sup>24</sup> Briefly, a ramp with 3 stopcocks was inserted in the drainage tubing connected to a Foley catheter. A standard infusion set was connected to a 1000-mL bag of saline and attached to the first stopcock. A 60-mL syringe was connected to the second stopcock, and the third stopcock was connected to a pressure transducer via rigid tubing. The system was flushed with saline to remove air, and the pressure transducer was zeroed at the symphysis pubis. To measure IAP, the bladder was completely emptied, and the urinary drainage tubing was clamped distal to the ramp device. The desired amount of 25 mL of saline was aspirated from the bag into the syringe and then instilled into the bladder. After opening the stopcocks to the pressure transducer, the IAP could be read from the bedside monitor. To confirm correct measurement, a rapid flush test, inspection of respiratory pressure variations and an oscillation test were performed before every measurement.

After the system was flushed, baseline IAP was measured without instilling extra volume. The IAP measurements were then obtained with 25 mL of saline. Each instillation was followed by a 1-minute equilibration period.<sup>24</sup>

Each patient underwent a repeated-measurement series. All measurements were obtained by the same observer to limit interobserver variability. Intra-abdominal hypertension was defined as an IAP greater than 12 mm Hg.<sup>24</sup>

Indocyanine green elimination tests were conducted concurrently using the LiMON, as described by Sakka.<sup>15</sup> Each patient received an ICG finger clip, which was connected to the monitor. A dose of 0.3 mg/kg of ICG (ICG-PULSION; Pulsion Medical Systems) was administered through a cubital fossa vein as a bolus and was immediately flushed with 10 mL of normal saline. The ICG-PDR measurements were calculated using the LiMON.

### Statistical analysis

We tested the normality distribution of variables using a 1-sample Kolmogorov–Smirnov test. The groups were compared using the Student *t* test for normally distributed data or the Mann–Whitney *U* test for non-normally distributed data. We compared baseline and twelfth-hour levels in each group using the Wilcoxon signed rank test. Changes from baseline to the twelfth-hour level were compared using analysis of covariance (ANCOVA) between the groups. We compared categorical variables using the  $\chi^2$  test. We considered results to be significant at  $p < 0.05$ . Results are expressed as means (and standard deviations; SDs) or number. We used Statistica 7.0 (Stat-Soft Inc.) software for our analyses.

### RESULTS

We followed 30 patients with an IAP greater than 12 mm Hg. Abdominal surgery was the most frequent underlying cause, followed by severe hemoperitoneum and severe abdominal infection (Table 1). Three patients with an IAP greater than 25 mm Hg underwent decompressive laparotomy, but these patients were not enrolled into the study.

The patients' sex, age, APACHE II and SOFA scores and length of stay in the ICU are shown in Table 1. There were no significant differences in age and sex between survivors and nonsurvivors.

Length of stay in the ICU was significantly different between the groups ( $p < 0.001$ ). The APACHE II scores were higher among nonsurvivors than survivors (26.88 [SD 7.42] v. 12.71 [SD 7.65],  $p < 0.001$ ), and the SOFA scores were also higher among nonsurvivors than survivors (18.1 [SD 1.3] v. 3.9 [SD 2.4],  $p < 0.001$ ).

The baseline IAP values were significantly higher

**Table 1. Demographic and clinical characteristics of critically ill patients with intra-abdominal pressure assessed using the LiMON**

Characteristic	Group; mean (SD)*		<i>p</i> value
	Survivors, <i>n</i> = 14	Nonsurvivors, <i>n</i> = 16	
Sex, female:male	8:6	9:7	0.96
Age, yr	61.00 (17.89)	67.38 (15.24)	0.35
Type of disease, no.			0.98
Abdominal surgery	7	8	
Severe hemoperitoneum	4	5	
Severe abdominal infection	3	3	
SOFA score	3.9 (2.4)	18.1 (1.3)	< 0.001
APACHE II score	12.71 (7.65)	26.88 (7.42)	< 0.001
Length of ICU stay, d	3.00 (1.88)	11.00 (8.03)	< 0.001

APACHE II = Acute Physiology and Health Evaluation; ICU = intensive care unit; LiMON = noninvasive liver function monitoring system; SD = standard deviation; SOFA = Sepsis-related Organ Failure Assessment.  
\*Unless otherwise indicated.

among nonsurvivors than survivors (19.38 [SD 2.09] mm Hg v. 13.07 [SD 0.99] mm Hg,  $p < 0.001$ ; Table 2). The twelfth-hour IAP values were higher than baseline measurements in the nonsurvivor group (21.50 [SD 1.96] mm Hg) and lower than baseline measurements in the survivor group (11.71 [SD 1.54] mm Hg). The difference between the groups was significant ( $p < 0.001$ ).

The baseline ICG-PDR values were significantly lower among nonsurvivors than survivors (10.86 [SD 3.35] % per min v. 25.51 [SD 6.78] % per min,  $p < 0.001$ ; Table 2). At the twelfth hour, ICG-PDR values were decreased in all groups. We detected significant differences between the groups ( $p < 0.001$ ).

The baseline AST values were significantly higher among nonsurvivors than survivors (258.56 [SD 84.19] mg/dL v. 128.07 [SD 28.32] mg/dL,  $p < 0.001$ ; Table 2). The twelfth-hour serum AST activities were higher than baseline measurements in the nonsurvivor group (326.50 [SD 93.74] mg/dL) and lower than baseline measurements in the survivor group (119.00 [SD 29.71] mg/dL). The difference between the groups was significant ( $p < 0.001$ ).

Baseline serum ALT activities were significantly higher among nonsurvivors than survivors (209.31 [SD 79.75] mg/dL v. 110.35 [SD 17.43] mg/dL,  $p < 0.001$ ; Table 2). The twelfth-hour serum ALT activities were higher than baseline measurements in the nonsurvivor group (267.56 [SD 87.00] mg/dL) and lower than baseline measurements in the survivor group (102.92 [SD 23.29] mg/dL). The difference between the groups was significant ( $p < 0.001$ ).

**DISCUSSION**

Our aim was to evaluate the effects of IAH on ICG-PDR using the LiMON in critically ill patients. Our results indicated that the baseline IAP values were significantly higher among nonsurvivors than survivors and that repeated IAP values were higher than baseline measurements in the nonsurvivor group and lower than baseline in the survivor group. The baseline ICG-PDR values were significantly lower among nonsurvivors than survivors, and repeated ICG-PDR values were decreased in both groups.

In critically ill patients, IAP is frequently elevated. Recent abdominal surgery, sepsis, organ failure, the need for mechanical ventilation, a 5-L net positive fluid balance in 24 hours and changes in body position are all associated with elevations in IAP.<sup>19</sup> Primary IAP (formerly termed surgical, postoperative or abdominal ACS) is characterized by the presence of acute or subacute IAH of relatively brief duration. It is most commonly encountered in patients with traumatic injuries or postoperatively.<sup>3,12</sup> Our patients had abdominal surgery, sepsis and a need for mechanical ventilation, and we believed that they had primary IAP.

Several previous studies reported the incidence and prognosis of IAP in critically ill patients.<sup>8,9</sup> Malbrain and colleagues<sup>8</sup> designed a multicentre, prospective epidemiologic study to assess whether IAP at admission was an independent predictor of mortality and to evaluate the effects of IAH on organ function. The authors reported that nonsurvivors had a significantly higher mean IAP on admission than survivors. They also concluded that the occurrence of IAH during a stay in the ICU was also an independent predictor of mortality. Vidal and colleagues<sup>9</sup> determined the epidemiology and outcomes of IAH in a heterogeneous ICU population and found that IAP was associated with mortality. In our study, we found that IAP was significantly higher and increased owing to repeated measurements among nonsurvivors compared with survivors.

Previous studies have demonstrated that the ICG-PDR can be used as an early indicator of hepatocellular injury.<sup>22,25</sup> Although the measurement of ICG-PDR was developed several years ago, a new transcutaneous pulse densitometry device that is less invasive and simpler to apply has recently been put to use in the clinical setting.<sup>15</sup> The only such device currently in use in Turkey is the LiMON. It is a user-friendly, noninvasive bedside system. Kimura and colleagues<sup>22</sup> examined whether ICG clearance is an early indicator of hepatocellular injury in septic shock and assessed its predictive value. They concluded that the ICG elimination rate constant can identify reversible liver injury early in the course of septic shock and that failure to reverse poor hepatic function within the first 24–120 hours correlates with poor outcome. In addition, Hemming and colleagues<sup>25</sup> reported ICG clearance to be a good predictor of successful

**Table 2. Baseline and twelfth-hour assessments in critically ill patients with intra-abdominal pressure assessed using the LiMON**

Measure	Group; time; mean (SD)						p value*
	Survivors, n = 14			Nonsurvivors, n = 16			
	Baseline	Twelfth hour		Baseline	Twelfth hour		
Intra-abdominal pressure, mm Hg	13.07 (0.99)	11.71 (1.54)†		19.38 (2.09)	21.50 (1.96)†		< 0.001
ICG-PDR, %/min	25.51 (6.78)	21.14 (3.84)†		10.86 (3.35)	8.50 (2.56)†		< 0.001
Aspartate aminotransferase, mg/dL	128.07 (28.32)	119.00 (29.71)†		258.56 (84.19)	326.50 (93.74)†		< 0.001
Alanine aminotransferase, mg/dL	110.35 (17.43)	102.92 (23.29)		209.31 (79.75)	267.56 (87.00)†		< 0.001

ICG-PDR = indocyanine green plasma disappearance rate; LiMON = noninvasive liver function monitoring system; SD = standard deviation.  
 \*Analysis of covariance.  
 † $p < 0.05$  for within-group comparison between baseline and twelfth-hour values.

hepatic resection in patients with cirrhosis. Patients with higher values had a significantly lower 30-day mortality.

The clinical value of ICG-PDR has already been demonstrated in various studies.<sup>26–28</sup> Wesslau and colleagues<sup>26</sup> reported that in liver transplantation, ICG-PDR may be used for evaluation of organ donors, as lower ICG-PDR values were associated with higher rates of discarded grafts in 41 patients. A borderline value for an ICG-PDR of 15% per minute was identified as suitable for transplantation. Krenn and colleagues<sup>27</sup> had shown the utility of ICG-PDR as an immediate and early test on graft function after liver transplantation. Oellerich and colleagues<sup>28</sup> found that ICG-PDR was the best predictor of prognosis in adult and pediatric patients for hepatic transplantation.

Previous human and animal studies demonstrated the effects of IAH on liver function.<sup>29–36</sup> In a paper by Malbrain,<sup>29</sup> hepatic arterial blood flow, portal venous blood flow and ICG-PDR clearance were all decreased during IAH. Bailey and Shapiro<sup>30</sup> concluded that impaired liver and gut perfusion had been demonstrated with elevation in IAP. Severe progressive reduction in mesenteric, arterial, portal and microcirculatory blood flow had been shown with graded elevation in IAP. Another 2 studies carried out by Diebel and colleagues<sup>31</sup> and Wendon and colleagues<sup>32</sup> concluded that even moderate levels of IAP were associated with impaired hepatocellular function. Michelet and colleagues<sup>33</sup> evaluated the type of support that modified IAP and ICG-PDR during prone positioning in patients with acute respiratory distress syndrome. They found that IAH was inversely correlated with ICG-PDR. Caldwell and Ricotta<sup>34</sup> conducted a study on dogs and found that elevated IAP caused a decrease in organ blood flow and may result in visceral ischemia and organ dysfunction. Hering and colleagues<sup>35</sup> investigated the effects of prone positioning on systemic hemodynamics, IAP and ICG-PDR. They found that IAP increased in the prone position but ICG-PDR did not differ between the 2 positions. Another study by Matejovic and colleagues<sup>36</sup> found no changes on ICG-PDR with the prone position. In our study, we found that the IAP levels were increased in nonsurvivors and decreased in survivors. The ICG-PDR levels were decreased in all groups.

Sakka and colleagues<sup>37</sup> classified patients into 4 groups according to their lowest ICG-PDR value. They found that mortality was about 80% in patients with ICG-PDR lower than 8% per minute and survival was about 80% in patients with ICG-PDR greater than 16% per minute.

A similar study conducted by our group<sup>38</sup> classified patients into 4 groups according to their lowest ICG-PDR value. We found that mortality was about 80% in patients with ICG-PDR lower than 8% per minute, 60% with ICG-PDR 8%–15% per minute and 27.3% in patients with ICG-PDR greater than 16%–24% per minute.

In the present study, we found that the repeated ICG-PDR values, as a marker of liver perfusion and function,

were decreased in both nonsurvivor and survivor groups. In the nonsurvivor group, the mean ICG-PDR decreased from 10.86 to 8.50, but the mean ICG-PDR decreased from 25.51 to 21.14 in the survivor group.

Sakka<sup>39</sup> presented the case of a 46-year-old man with chronic heart failure due to dilate cardiomyopathy, with increased IAP due to ascites. The first IAP was 18 mm Hg, and after ascites removal the IAP decreased to 12 mm Hg. The baseline ICG-PDR was 11.6% per minute, and repeated ICG-PDR values after removal of the ascites were 15.6% per minute. The author concluded that the increase in ICG-PDR may indicate an increase in hepatic blood flow that resulted from decompression of the abdomen by paracentesis. Another report by the same author<sup>40</sup> presented the case of a 67-year-old woman who underwent laparotomy for an acute abdomen and developed septic shock. Abdominal compartment syndrome developed over the following 6 hours, during which the ICG-PDR had decreased from 22.2% per minute to 12% per minute. Her IAP, as measured by the urinary bladder filling technique, was 32 mm Hg. After reoperation, ICG-PDR improved significantly. The author concluded that ICG-PDR monitoring in hepato-splanchnic blood was useful in patients with ACS.

## CONCLUSION

Measurement of ICG-PDR with the LiMON is a good predictor for determining the effects of IAP on liver function. Thus, it can be recommended for evaluation of critically ill patients.

**Competing interests:** None declared.

**Contributors:** All authors helped design the study, write and review the article and approved it for publication. Drs. Inal, Memis, Sezer, Atalay and Karakoc acquired the data, which Dr. Sut analyzed.

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