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Low values of left ventricular ejection time in the post-anhepatic phase may be associated with occurrence of primary graft dysfunction after orthotopic liver transplantation: results of a single-centre case-control study

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Abstract. – BACKGROUND: Previous investigations on risk factors for orthotopic liver transplantation (OLT) surgery have not analyzed hemodynamic aberrations in great detail. Moreover, the usefulness of esophageal Doppler monitoring has not been extensively studied in this clinical setting. The aim of this study was to evaluate if the occurrence of primary graft dysfunction (PGD) may be anticipated by hemodynamic indexes measured by esophageal Doppler (ED) monitoring system as well as by pulmonary artery catheter (PAC) in patients undergoing OLT.

MATERIALS AND METHODS: 38 OLT recipients were studied. Patients with acute liver failure or having non treated esophageal varices and those transplanted with marginal donors were excluded from the study. The haemodynamic data – measured by ED monitoring system (HemosonicTM 100, Arrow, OK, USA) and PAC – collected at the following 3 time points were considered for statistical analysis: 30 minutes after the induction of anesthesia but before skin incision, T0; 20 minutes after liver dissection, T1; at the beginning of biliary reconstruction, T2. On the basis of early outcome (72 hours after OLT), patients were distinguished into two groups: those with PGD (grade III-IV of Toronto classification) and those without PGD (grade I-II).

RESULTS: LVETc (left ventricular ejection time) values, registered at the beginning of biliary reconstruction (T2), were lower in patients with PGD compared to those without PGD ($p < 0.000$), while there were no differences in hemodynamic parameters derived from PAC between the two groups.

CONCLUSIONS: Since LVETc is related to preload, the results of this study would suggest that normovolemia could be the end point of a fluid replacement strategy in OLT setting.

Key Words:
Primary graft dysfunction, Orthotopic liver transplantation, Hemodynamic indexes, Esophageal Doppler monitoring.

Introduction

Hemodynamic monitoring plays a vital role in the management of cirrhotic patients undergoing orthotopic liver transplantation (OLT). In this regard, maintaining a high cardiac output (CO) in liver transplant recipients is essential in order to ensure adequate tissue perfusion and to improve graft survival[1,2].

To date, pulmonary artery catheter (PAC) remains the gold standard of hemodynamic monitoring and the introduction of the new generation of catheters has gained renewed interest in its reliability due to the possibility of continuously measuring cardiac output or index, right ventricular ejection fraction, and right ventricular end diastolic volume index[3-5]. Filling pressures (central venous pressure and pulmonary artery occlusion pressure) are the standard hemodynamic parameters routinely used to make decisions regarding fluid therapy, even if there are no consistent answers in literature regarding the best way for optimizing fluid therapy and, therefore, CO in critically ill patients, as well as in cirrhotic patients undergoing OLT.

In the past years, a minimally invasive haemodynamic monitoring system, such as esophageal

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Doppler (ED), has led us to take into account new parameters that may be indicative of cardiac inotropism and preload, such as mean acceleration (MA), peak velocity (PV) and left ventricular ejection time (LVETc)[6]. The use of these parameters in the perioperative period, has been shown to improve patients' outcome in several clinical settings[6-10]. However, the usefulness of esophageal Doppler monitoring has not been extensively studied in cirrhotic patients undergoing OLT[11-13]. As the occurrence of primary graft dysfunction (PGD) may be harmful for patient and/or graft survival, the chance of a prompt detection of this clinical condition may be of great importance[14].

This prospective observational study was designed to evaluate if intraoperative indexes measured by ED monitoring system as well as by PAC could predict the occurrence of PGD assessed 72 hours following liver transplantation.

Materials and Methods

After obtaining Local Ethics Committee approval, 38 patients who underwent OLT were included in the study. Acute liver failure, transplantations with marginal donors and the presence of non treated esophageal varices were the criteria to exclude patients from the study. Marginal liver donor criteria included the following: (1) age >65 years; (2) cold ischemia time >12 hours; (3) steatosis >30%; (4) inotropic support; (5) organ recovery from non heart-beating donors; (6) "split-liver" donation.

Standard monitoring consisted of 2-lead electrocardiography (II/V5), pulse oximetry, direct arterial pressure monitoring (radial artery catheter), multigas analysis and pulmonary artery catheterization (Opticath, Abbott, North Chicago, IL, USA). General anaesthesia was induced using intravenous thiopental (3 mg/kg), fentanyl (2-3 mcg/kg) and rocuronium (0.6 mg/kg) Maintenance was performed with sevoflurane and remifentanil in continuous infusion (as required). Muscular blockade was achieved by using cisatracurium besilate at a rate of 1.5-3 mcg/kg/h. Patients were ventilated with a Tidal Volume of 6-8 ml/kg, Respiratory Rate 10-14 in order to achieve an $EtCO_2$ of 30-35. Venovenous bypass (VVBP) was used in all the cases.

Allon™ 2001 thermowrap (Mtre advanced technology ltd, Yavne, IS), warmed fluids, and a forced-air warming device (Bair Hugger Model 505, Arizant Healthcare Inc, MN, USA) were used to maintain patients' core temperature within the normal range.

The ED probe (Hemosonic TM – Arrow, OK, USA) was gently inserted orally after tracheal intubation and was advanced until its tip was located in the mid-esophagus (third intercostal space), as previously described[15].

The Doppler signal was judged more or less optimal, according to: (1) optimal ultrasound view of aortic walls; (2) highest value of aortic velocity. Moreover, taking into account the respiratory changes in stroke volume, the ED monitor was preset to calculate CO by averaging stroke volume over 20 heart beats.

Haemodynamic data collected at 3 time points were considered for statistical analyses: 30 minutes after the induction of anesthesia but before skin incision (T0), 20 minutes after liver removal during anhepatic phase (T1) and finally at the beginning of biliary reconstruction during post-anhepatic phase (T2). The hemodynamic data were: PAOP (pulmonary artery occlusion pressure), CVP (central venous pressure), SVR (systemic vascular resistances), CO from Swan Ganz catheter (COs); and LVETc (left ventricular ejection time), PV (peak velocity), ACC (acceleration), CO from Hemosonic monitoring system (COh).

Fluid therapy and vasoactive administration were performed on the basis of standard haemodynamic derived from PAC; each major hemodynamic change (more than 20% of baseline values) was counteracted by fluid therapy and/or by vasoactive drugs administration (norepineprine 0.01-0.05 mcg/kg/min or dobutamine 5-8 mcg/kg/min). In addition, we aimed at 10 g/dl of hemoglobin value through packed red cell infusions and cell-salvaged blood. For recipients evaluation, liver decompensation was measured by using the model for end-stage liver disease (MELD) score[16].

In order to assess the primary graft dysfunction (PGD), the classification of liver function degree from Toronto Summit was used. It includes the following parameters: aminotransferase activity, bile production, and coagulapathy during the 72 hours after transplantation. The liver function was grouped into four grades. In a grade I, AST remained below 1000 U/L, there was a bile production > 40 mL/day, and coagulation improved. In a grade II, initial AST level exceeded 1000 U/L, but fell over the subsequent 48 hrs with improved coagulation and bile flow > 40 mL/day. In a grade III, AST overcame 2500 U/L

for the first 48 hrs, bile production was reduced (> 40 mL/day), and coagulopathy was more severe. In grade IV, there were rapidly rising AST levels with no bile production and severe coagulopathy. Primary outcome was considered positive for patients showing grade I-II of Toronto classification (good graft function) or negative in patients with grade III-IV (PGD)[14].

Statistical Analysis

On the basis of early outcome (72 hours after OLT), patients were distinguished into two groups: those with PGD (grade III-IV of Toronto classification) and those without PGD (grade I-II). Descriptive statistics (means ± standard deviations or numbers) were used for patients' characteristics: student t test or Fisher test were used on absolute values to compare patients with PGD (n=7) and those without PGD (n=31). Multivariate analyses of variance – repeated measures – (MANOVAs: Rao r) were performed on the following dependent variables: hemodynamic data obtained from Swann-Ganz catheter (COs, PAOP, CVP, SRV), variables derived from Hemosonic (COh, ACC, LVETc, PV) and hemodynamic data obtained from invasive arterial monitoring (heart rate: HR and mean arterial pressure: MAP).

Univariate analysis of variance with intervals as repeated measures was used on time related measurements for each single dependent variable. Post-hoc comparisons were performed using Student's *t*-test. Logistic regression was used to determine possible predictors for negative outcome (PGD) to occur. Statistical significance for the inclusion of variables in the regression model was considered at the 0.05 level.

Statistical analyses were carried out using Statistica Version 6.1 software (StatSoft, Tulsa, OK, USA) and Epi Info™ Version 3.4 (Atlanta, GA, USA).

Results

Table I shows the characteristics of patients with and without PGD. Estimated blood loss (EBL) and intensive care unit (ICU) stay were significantly higher in patients showing PGD 72 hours after OLT.

As seen in Table II, Manova did not show significant effects for hemodynamic variables derived from Swann Ganz. Anovas on single dependent variables demonstrated that there was an effect of the time on CVP [Fisher F: (2,72): 6.8; $p = 0.002$]. Single post-hoc comparisons revealed that CVP measured at T0 was greater than CVP at T1 in both groups. Moreover, Anova on PAOP showed a significant effect of time [Fisher F: (2,72): 4.4; $p = 0.02$]. Single post-hoc comparisons revealed that PAOP registered at T0 was greater than PAOP at T1 and T2 only in the group of patients without PGD.

Manova on variables derived from Hemosonic did not show significant effects. Anovas on single variables revealed that, only on LVETc, there were effects of PGD [Fisher F: (1,36): 6.8; $p = 0.01$], time [Fisher F: (2,72): 5.1; $p = 0.009$] and PGD per time [Fisher F: (2,72): 5.4; $p = 0.007$] (Table III, Figure 1). Post-hoc comparisons revealed that LVETc decreased at T2 when compared to value registered at T1 in both groups,

Table I. Characteristics of the patients with and without primary graft dysfunction. The values are mean ± standard deviation or numbers.

	Patients having PGD (n = 7)	Patients without PGD (n = 31)
Age, yrs	51 ± 9	54 ± 8
Gender, n (M/F)	5/2	18/13
MELD score	21.6 ± 8.0	17.3 ± .6.1
Estimated blood loss (ml)*	6488 ± 8058	2895 ± 2022
Primary liver disease, n		
Chronic viral hepatitis	3	14
Primary biliary cirrhosis	1	2
Cryptogenic cirrhosis	1	2
Potus related cirrhosis	2	12
Wilson's disease	0	1
ICU stay (days)*	11.5 + 6.2	5.8 + 2.4
Vasoactive drug (n) at the end of surgery	7 (100%)	6 (20%)

*$p < 0.05$.

Table II. Haemodynamic data obtained from Swann-Ganz catheter in patients with and without primary graft dysfunction (PGD) . The values are mean ± standard deviation. MANOVA analysis (df); RaoR; *p*: PGD: (4,33): 0.5; *p* = NS; TIME: (8,29): 2.2; *p* = NS; PGD per TIME: (8,29): 0.8; *p* = NS.

		T0	T1	T2	Significant post-hoc comparisons
COs (L/min) ANOVA analysis (df); Fisher F; *p*: PGD: (1,36): 1.7; *p* = NS TIME: (2,72): 0.3; *p* = NS PGD per TIME: (2,72): 2.1; *p* = NS	Patients having PGD (n = 7)	9.5 ± 1.5	10.6 ± 1.5	9.1 ± 2.2	
	Patients without PGD (n = 31)	8.7 ± 2.7	8.2 ± 2.8	8.9 ± 2.5	
CVP (mmHg) ANOVA analysis (df); Fisher F; *p*: PGD: (1,36): 0.3; *p* = NS TIME: (2,72): 6.8; *p* = 0.002 PGD per TIME: (2,72): 0.4; *p* = NS	Patients having PGD (n = 7)	11.1 ± 1.7	7.1 ± 2.5	9.0 ± 1.4	T0 vs T1*
	Patients without PGD (n = 31)	10.7 ± 3.2	8.3 ± 3.5	9.5 ± 2.8	T0 vs T1**
PAOP (mmHg) ANOVA analysis (df); Fisher F; *p*: PGD: (1,36): 0.1; *p* = NS TIME: (2,72): 4.4; *p* = 0.02 PGD per TIME: (2,72): 0.0; *p* =NS	Patients having PGD (n = 7)	14.7 ± 2.1	12.0 ± 4.8	11.7 ± 1.9	
	Patients without PGD (n = 31)	14.9 ± 3.8	12.5 ± 4.2	12.2 ± 3.6	T0 vs T1* T0 vs T2**
SRV (dine/sec/cm^5) ANOVA analysis (df); Fisher F; *p*: PGD: (1,36): 1.1; *p* = NS TIME: (2,72): 0.2; *p* = NS PGD per TIME: (2,72): 0.8; *p* = NS	Patients having PGD (n = 7)	735 ± 108	669 ± 127	736 ± 212	
	Patients without PGD (n = 31)	790 ± 194	804 ± 273	772 ± 158	

*$p < 0.05$; **$p < 0.01$.

and when compared to value at T0 only in the group of patients with PGD; LVETc, measured at T2, was also lower in patients with PGD compared to patients without PGD.

Manova on haemodynamic data obtained from invasive arterial monitoring showed an effect of time on HR in patients with and without PGD. There were no significant differences in HR and MAP values between the two groups at each time. In both groups HR was significantly greater at T1 and T2 compared to baseline values (T0); in patients without PGD, HR at T2 was higher compared to values registered at T1 (see Table IV). In patients without PGD, MAP decreased at T1 and T2 compared to T0.

Logistic regression in Table V showed that PGD was less probable to occur in patients with greater LVETc values registered at T2.

The area under the ROC curve of the logistic regression model was 0.80 (Figure 2).

Discussion

Many studies have demonstrated the usefulness of hemodynamic indexes derived from ED in critically ill patients[17-19]. In a recent randomized trial, Sinclair and colleagues showed that patients with femoral neck fracture undergoing intravascular colloid resuscitation, guided by transesophageal Doppler during surgical repair, had a significantly reduced hospital stay (39%) compared with control subjects[20]. However, none of these studies has addressed the association of postoperative graft function and Doppler-derived parameters in patients undergoing liver transplantation. In our study, a short period after OLT was chosen as with the passing of time this procedure may be more affected by the huge number of factors that influence outcome of these critically ill patients. In addition, we decided to exclude from the study patients who received graft from "marginal" donors

Table III. Haemodynamic data obtained from Hemosonic monitoring system in patients with and without primary graft dysfunction (PGD). The values are mean ± standard deviation. MANOVA analysis (df); RaoR; *p*: PGD: (4,33): 2.0; *p* = NS; TIME: (8,29): 1.6; *p* = NS; PGD per TIME: (8,29): 2.0; *p* = 0.08.

		T0	T1	T2	Significant post-hoc comparisons
COh (L/min) ANOVA analysis (df); Fisher F; *p*: PGD: (1,36): 0.3; *p* = NS TIME: (2,72): 0.04; *p* = NS PGD per TIME: (2,72): 0.2; *p* = NS	Patients having PGD (n = 7)	7.2 ± 1.9	7.3 ± 2.7	7.1 ± 2.2	
	Patients without PGD (n = 31)	7.9 ± 2.9	7.5 ± 2.6	7.8 ± 2.5	
LVETc (ms) ANOVA analysis (df); Fisher F; *p*: PGD: (1,36): 6.8; *p* = 0.01 TIME: (2,72): 5.1; *p* = 0.009 PGD per TIME: (2,72): 5.4; *p* = 0.007	Patients having PGD (n = 7)	348 ± 36	327 ± 43	296 ± 60	T0 vs T2**; T1 vs T2*
	Patients without PGD (n = 31) *p* value	357 ± 22 NS	343 ± 37 NS	356 ± 3 4 0.000004	
ACC (m*s-2) ANOVA analysis (df); Fisher F; *p*: PGD: (1,36): 0.05; *p* = NS TIME: (2,72): 1.1; *p* = NS PGD per TIME: (2,72): 1.6; *p* = NS	Patients having PGD (n=7)	21 ± 9	27±6	24 ± 8	
	Patients without PGD (n=31	24 ± 13	23±11	29 ± 18	
PV (cm/s) ANOVA analysis (df); Fisher F; p: PGD: (1,36): 0.01; *p* = NS TIME: (2,72): 0.7; *p* = NS PGD per TIME: (2,72): 0.4; *p* = NS	Patients having PGD (n = 7)	79 ± 15	81 ± 21	85 ± 22	
	Patients without PGD (n = 31)	83 ± 32	77 ± 23	83 ± 29	

*$p < 0.05$; **$p < 0.01$.

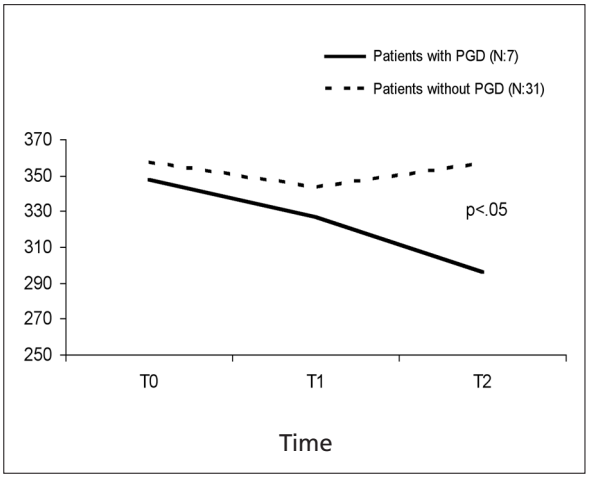

Figure 1. Anova PGD (patients with PGD; patients without PGD) per TIME (T0; T1; T2) on LVETc. (df) Fisher F: PGD: (1,36): 6.8; *p* = 0.01. TIME: (2,72): 5.1; *p* = 0.009 PGD per TIME: (2,72): 5.4; *p* = 0.007.

in order to mainly focus the analysis on recipients' clinical problems; in this respect, we did not find any differences in preoperative MELD score between patients with and without PGD.

In the current study, we found a relationship between recipients' early outcome and a Doppler derived parameter, i.e. LVETc. Particularly, the main result of this study was that low LVETc values at the end of transplantation were associated with the occurrence of PGD. All the other hemodynamic parameters, derived from PAC as well as from ED, failed to be significantly related to early patient outcome. Moreover, in keeping with literature data, we found that the estimated blood losses played a role in determining PGD.

The potential for massive and rapid blood loss during OLT acts as a heavy challenge for the anaesthesiologists and it has been clearly demonstrated that it may significantly affect pa-

Table IV. Haemodynamic data obtained from invasive arterial monitoring in patients with and without primary graft dysfunction (PGD). The values are mean ± standard deviation. MANOVA analysis (df); RaoR; *p*: PGD: (2,35): 0.02; *p* = NS; TIME: (4,33): 8.4; *p* = 0.00009; PGD per TIME: (4,33): 0.7; *p* = NS.

		T0	T1	T2	Significant post-hoc comparisons
MAP (mmHg) ANOVA analysis (df); Fisher F; *p*: PGD: (1,36): 0.04; *p* = NS TIME: (2,72): 4.5; *p* = 0.014 PGD per TIME: (2,72): 0.3; *p* = NS	Patients having PGD (n = 7)	84.8 ± 10.3	82.2 ± 7.6	78.6 ± 8.5	
	Patients without PGD (n = 31)	86.6 ± 8.9	80.8 ± 9.6	79.8 ± 7.4	T0 vs T1** T0 vs T2**
HR (b/min) ANOVA analysis (df); Fisher F; *p*: PGD: (1,36): 0.01; *p* = NS TIME: (2,72): 10.9; *p* = 0.00007 PGD per TIME: (2,72): 0.9; *p* = NS	Patients having PGD (n=7)	78.4 ± 8.7	90.0 ± 6.4	93.6 ± 8.1	T0 vs T1* T0 vs T2**
	Patients without PGD (n=31)	82.5 ± 11.3	87.2 ± 12.3	92.0 ± 9.9	T0 vs T1* T0 vs T2** T1 vs T2*

*$p < 0.05$; **$p < 0.01$.

Table V. Logistic regressions results showing the incidence of primary graft dysfunction when related to LVETc and estimated blood loss (EBL).

2*log-likelihood (likelihood ratio; p)	Variable	Odds ratio	C.I.	Coefficient	S. E.	Z-statistic	p value
Model (primary graft dysfunction): 26.41 (9.90; $p < 0.01$)	LVETc	0.97	0.94-0.99	-0.03	0.01	-2.10	0.03
	EBL	1.00	0.99-1.00	0.00	0.00	0.26	0.79

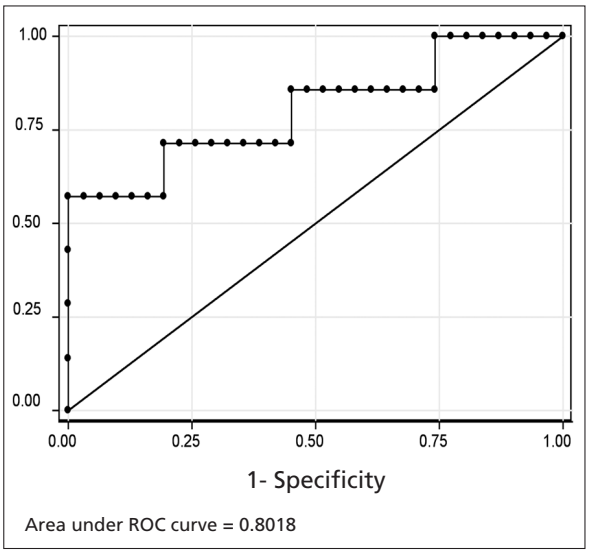

Figure 2. ROC curve after logistic regression reporting sensitivity and 1- specificity of predicting parameter (LVETc) for outcome.

tient outcome[21]. However, until now, there has been no agreement in literature on the most appropriate hemodynamic parameter which could reflect the efficacy of fluid therapy, and above all on what level of fluid replacement may be advisable in OLT setting. Filling pressures, such as central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP), are the most common investigated preload indexes, even if many studies have demonstrated their unsuitability in mirroring real volemia[22-24]. In addition, there are conflicting results in literature about the best filling pressure level to be achieved. Massicotte et al[25] suggested that maintaining a low CVP minimizes blood loss during the dissection phase of OLT and reduces the need for blood transfusion with consequent positive effects on patients' outcome. However, it has been suggested by other Authors that lowering CVP impairs tissue perfusion of various organs, par-

ticularly of the kidneys, increasing post-transplant renal dysfunction and 30-day mortality regardless of the amount of blood product transfusion[26]. By now, only one study addressed the issue of the effect of filling pressure (CVP) on postoperative graft function[27]. These Authors concluded that maintaining a lower PVC during the post-anhepatic phase of OLT is not associated with any benefit in terms of immediate postoperative graft function, graft survival or patient survival. Moreover, another recent study on this subject did not find any relationship between intraoperative hemodynamic data and recipients' one month outcome[28].

In our study, filling pressures derived from PAC did not show any correlation between post-anhepatic phase values and early outcome. On the contrary, as previously stated, we found significant lower LVETc values during post-anhepatic phase in patients with PGD than in those without PGD: patients who exhibited postoperative bad graft function had mean LVETc values below the normal range, while patients with adequate graft recovery showed LVETc values within normal range. LVETc is claimed to indicate preload and to allow the assessment of fluid responsiveness in hypovolemic patients[29]. In this respect, a study suggests that the LVETc is superior to pulmonary artery wedge pressure in predicting preload[30]. However, as the LVETc is inversely related to systemic vascular resistance, a shortened LVETc may also indicate a preload-independent vasoconstriction, for example, due to hypothermia and vasopressors[31]. We can argue that, in our study, patients with PGD might have suffered from hypovolemia, due to the significantly higher estimated blood loss observed in this group and in spite of quite normal other hemodynamic parameters. It would appear to be that an occult hypovolemia, counteracted by a more frequent use of vasoactive drugs, might have affected the early outcome of recipients due to a reduced blood flow to splancnic organs and particularly to the graft. We cannot be certain whether or not a lower LVETc has been the direct cause of PGD as other non considered factors could have been contribute to this association. Furthermore, this study cannot prove that prevention or early correction of this hemodynamic aberration would lead to a different outcome. Another limitation of this investigation is the small numbers of recipients studied partly due to the restricted inclusion/exclusion criteria.

Conclusions

Even if further studies are requested, the results of this report suggest that normovolemia should be the end point of a fluid replacement strategy in liver transplantation setting. As a consequence, low preload indexes should be avoided in liver recipients, at least after reperfusion of the graft. Moreover, our findings underline the need of other parameters, in addition to the standard ones, that may reveal an impairment of splanchnic perfusion, and may suggest an expansion of the anesthesiological role in perioperative liver protection.

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