Effects of Different Positive End-Expiratory Pressure Values on Liver Function and Indocyanine Green Clearance Test in Liver Transplantation Donors: A Prospective, Randomized, Double-Blind Study

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ABSTRACT

Introduction. The aim of this study was demonstrate the influence of different positive end-expiratory pressure (PEEP) values on blood flow of the liver by indocyanine green (ICG) clearance test in donor patients.

Methods. ICG clearance tests were conducted concurrently using a noninvasive monitor that tracks the plasma disappearance rate of ICG (PDR-ICG%/min) and 15-minute retention rate after administration of ICG (ICG-R15%). This study was performed in 40 patients who underwent right hepatectomy.

Results. The positive end-expiratory pressure (PEEP) was 0 cm H_20 in the first (control) group (group K) and 10 mm Hg in the second study group (group P). ICG clearance test values before general anesthesia (T0), after induction of general anesthesia (T1), after transection (T2), 24 hours postoperative (T3), and 72 hours postoperative (T4) were recorded. Simultaneously, hemoglobin (Hgb), hematocrit (Hct), platelet count, plasma levels of prothrombin (PT), International Normalized Ratio (INR), total bilirubin, direct bilirubin, albumin, aspartate aminotransferase, and alanine aminotransferase values were analyzed. In terms of the plasma disappearance rate and retention rate of ICG 15 minutes after administration, significant difference was not observed between groups. PT and INR values were different within comparisons groups ($P < .05$). There were significant differences in Hgb and Hct values compared with the baseline values (T0) within group (T1, T2, T3, T4) measurements and between group comparisons at T0 and T4 ($P < .05$). Systemic arterial pressure, mean arterial pressure, and central venous pressure were significantly different between the groups ($P < .05$).

Conclusions. Given the small magnitude and limited clinical significance of these changes, we conclude that PEEP values between 0 and 10 cm H_2O have no effect on global liver function and liver-related liabilities tests in patients undergoing elective liver donor surgery.

DONORS ARE VOLUNTEERS without any health problems. Therefore, safety of the anesthesia method and donors is important [1]. It is known that different positive end-expiratory pressure (PEEP) values applied during and after the operation to the recipients of liver transplant affects graft function by changing hepatic and portal blood flow owing to its effect on hemodynamics and splenic perfusion [2]. In addition, PEEP values of >15 cm H_2O disrupt venous return and have negative affects on venous flow of the liver [3].

Indocyanine green (ICG) is a nontoxic, water-soluble triacarbocyanime dye. An ICG clearance test has been largely used to measure the hepatic function and the hepatic blood

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flow for the last 3 decades [4]. ICG clearance reflects many important functional parameters of the liver containing clearance and carrier capacity owing to blood flow. Recently, with the LiMON system (Impulse Medical System, Munich, Germany), the ICG elimination rate is monitored by a noninvasive pulse-densitometric method [5]. This monitor expresses the ICG elimination in terms of plasma disappearance rate of ICG (PDR-ICG) and the retention rate of ICG minutes after administration (ICG-R15) [5].

Graft function is influenced by many factors, including hemodynamic parameters and blood flow of the organ in liver transplant patients. The goal of this study was demonstrate the influence of different PEEP values on blood flow of the liver and liver function in liver transplant donors with liver function tests and ICG clearance test and to determine optimal intraoperative PEEP values.

METHODS

This study was performed between January and July 2013 and included 40 patients between the ages of 18 and 55 in American Society of Anesthesiologists groups I and II who have undergone general anesthesia for liver donation right hepatectomy at the Inönü University Faculty of Medicine, Department of Anesthesiology and Reanimation. Consent of Malatya Clinical Research Ethical Board numbered 2013/08 and consent from each patient were obtained.

Electrocardiography, peripheral oxygen saturation, and noninvasive blood pressure were monitored in patients admitted to the operating room to establish baseline values. ICG clearance test in terms of PDR-ICG and retention rate of ICG minutes after administration (ICG-R15) measurements were performed to provide basal value before the application of any anesthetic intervention and were recorded. An ICG (Pulsion Medical Systems, Munich, Germany) dose of 0.5 mg/kg bodyweight was bolus injected into the antecubital vein. The clearance was measured using the LiMON densitometer before the operation. We prospectively divided into 2 groups, PEEP was 0 cm H_2O in the first (control) group (group K) and PEEP was 10 mm Hg in the second study group (group P). We included 20 patients in each group of this study. Anesthesia was administered to all patients using a standardized technique. Maintenance of anesthesia was with balanced anesthesia to keep bispectral values between 40 and 60. All patients were ventilated to attain an end-tidal carbon dioxide value of 35–40 mm Hg. Invasive arterial blood pressure monitoring from the radial artery at the nondominant side. Three-way 7.5-Fr central venous catheter was placed into the jugular vein of all patients to obtain central venous pressure (CVP). Pringle maneuver was recorded. The centers' protocol for total portal occlusion is 15-minute occlusion alternated with 5-minute reperfusion for patients with normal liver parenchyma. Observed complications were recorded during the operation.

The PDR-ICG and the R15-ICG hemodynamic status (systolic, diastolic, mean arterial pressure [MAP], CVP, and heart rate), hemoglobin (Hgb), platelet count, and standard liver biochemistry (plasma levels of prothrombin [PT], International Normalized Ratio, albumin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, and direct bilirubin) were increased before induction of general anesthesia (T0), immediately after the end of surgery (T1), and 24 and 72 hours after liver transection (T2, T3, T4).

Statistical Analyses

SPSS 16.0 package program was used in the statistical analysis of the data [6]. With Kolmogorov–Smirnov normality test, data belonging to quantitative variables were determined to show normal distribution ($P > .05$). A paired t test was used to test the change in data over the course of time. An independent t test was used in the intergroup comparisons. Data belonging to quantitative variables were given as mean values ± standard deviation (SD), data belonging to qualitative variables were given as number (n) and percentage (%). $P < .05$ was considered significant.

Table 1. Patient Demographics and Characteristics

Variable	Group K (n = 20)	Group P (n = 20)	P
Age (y)	27.5 ± 7.5	26.5 ± 7.8	.523
Gender (M/F)	16/4	12/8	.399
Height (cm)	172.1 ± 7.5	169.2 ± 8.2	.802
ASA I/II (n)	5/15	14/6	.245
Weight (kg)	69.9 ± 8.9	69.1 ± 7.8	.696

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; Group K, PEEP 0 mm Hg; Group P, PEEP 10 mm Hg; PEEP cm H_2O, positive end-expiratory pressure.
Values are means ± standard deviation (SD) or number.

RESULTS

No difference was found between the groups in respect to demographic properties of the patients ($P > .05$; Table 1). We found no difference in surgical characteristics of the patients between groups apart from in bleeding in the group P (Table 2). No difference between groups was seen with respect to the Pringle maneuver ($P > .05$; Table 2). Serum Hgb, Htc, PT, and AST values were significantly higher on postoperative day 3 in group K than in group P ($P < .05$; Table 3). We observed statistical differences in the evolution of the hemodynamic changes (systolic, diastolic, mean arterial pressure, and CVP) measured between the studied groups ($P < .05$; Table 4). When groups were compared for PDR and R15, no difference was observed between the groups (Table 5).

DISCUSSION

In our study, a PEEP of 0 or 10 during hepatectomy in liver donors did not effect liver function tests and ICG clearance test. We have observed that PDR and R15 values were similar in patients ventilated with PEEP 0 or 10 cm H_2O.

In previous studies, PEEP at physiologic levels did not have a clinical effect until 10–15 cm H_2O; however, it disrupted liver function [7]. Given the proximity of 5 to this physiologic

Table 2. Surgical Characteristics of the Donors

Variable	Group K (n = 20)	Group P (n = 20)	P
Duration of anesthesia (min)	396 ± 83	353 ± 71	.393
Duration of surgery (min)	345 ± 80	305 ± 74	.921
Urine output (mL)	1086 ± 477	1062 ± 497	.878
Temperature (°C)	36.8 ± 0.7	36.6 ± 0.7	.784
Remnant KC (%)	32 (28–40)	33 (29–40)	.883
Bleeding volume (mL)	298 ± 75	330 ± 114	.006
Graft weight (g)	773 ± 142	734 ± 108	.379
Pringle maneuver (min)	19.5 (12–28)	23.8 (10–30)	.268

Abbreviations: Group K, PEEP 0 mm Hg; Group P, PEEP 10 mm Hg; PEEP, positive end-expiratory pressure.
Values are mean ± standard deviation (SD) or n (range).

Table 3. Laboratory Values

Parameter	T0	T1	T2	T3	T4
Hemoglobin					
Group K	15.1 ± 1.9	13.9 ± 2.1*	13.6 ± 2.4*	14.1 ± 2.1*	13.5 ± 2.2*
Group P	14.4 ± 1.7†	13.3 ± 1.6*	12.4 ± 1.7*	13.6 ± 1.7*	12.4 ± 1.3*†
Hematocrit					
Group K	44.1 ± 4.9	40.6 ± 5*	39.5 ± 5.5*	40.1 ± 5.3*	39.3 ± 6.2*
Group P	43.1 ± 4.8†	39.6 ± 4.7*	36.7 ± 5.2*	38.8 ± 4.6*	36.1 ± 3.1*†
Thrombocyte					
Group K	259 ± 60	232 ± 59*	226 ± 45*	216 ± 42*	197 ± 42*
Group P	267 ± 59	254 ± 71*	246 ± 67*	223 ± 69*	195 ± 59*
Plasma levels of prothrombin					
Group K	13.6 ± 1.2	13.9 ± 1.3	14.9 ± 1.8*	21.4 ± 3,7*	18.5 ± 2.6*†
Group P	13.3 ± 0.6	13.8 ± 0.9*	16.1 ± 5.5*	19.8 ± 6,7*	16.9 ± 1.5*
International Normalized Ratio					
Group K	1.05 ± 0.11	1.1 ± 0.11*	1.2 ± 0.16*	1.9 ± 0.37*	1.5 ± 0.23*†
Group P	1 ± 0.06	1.1 ± 0.13	1.3 ± 0.66*	1.8 ± 0.65*	1.4 ± 0.15*
Albumin					
Group K	4.2 ± 0.3	3.7 ± 0.3*	3.2 ± 0.4*	3.2 ± 0.3*	3.2 ± 0.3*
Group P	4.2 ± 0.2	3.6 ± 0.4*	2.9 ± 0.4*	3.2 ± 0.5*	3.2 ± 0.2*
Total bilirubin					
Group K	0.5 ± 0.3	0.7 ± 0.3*	1 ± 0.4*	2.7 ± 1.8*	3.1 ± 2.4*
Group P	0.6 ± 0.4	0.7 ± 0.4*	1 ± 0.5*	2.6 ± 1.1*	2.3 ± 1.3*
Direct bilirubin					
Group K	0.2 ± 0.1	0.3 ± 0.1*	0.5 ± 0.2*	0.8 ± 0.7*	1.5 ± 1.3*
Group P	0.2 ± 0.1	0.3 ± 0.1*	0.4 ± 0.2*	0.8 ± 0.3*	1 ± 0.6*
Aspartate aminotransferase					
Group K	19 ± 4.5	36 ± 26	132 ± 87*	206 ± 78*	109 ± 39*
Group P	18 ± 3.7	35 ± 36	117 ± 43*	193 ± 95*	86 ± 22*†
Alanine aminotransferase					
Group K	19 ± 11	39 ± 35	121 ± 87*	213 ± 107*	140 ± 75*
Group P	18 ± 6	34 ± 38	111 ± 43*	216 ± 118*	125 ± 49*

Abbreviations: Group K, PEEP 0 mm Hg; Group P, PEEP 10 mm Hg; PEEP, positive end-expiratory pressure.
Values are mean ± standard deviation (SD).
*Variation according to T0 ($P<.05$).
†Intergroup variation ($P < .05$).

PEEP level, we chose 10 cmH_2O because the upper limit of PEEP—at 15 cm H_2O—disrupted liver functions.

In the ICG and hemodynamic changes study by Claus et al [8] in patients who have undergone liver transplantation, a PEEP value of 5 or 10 showed no difference, similar to our study. However, a significant decrease in the cardiac index and oxygen presentation was detected compared with a PEEP of 0 cm H_2O. In an animal study by Matuschak et al [9], a PEEP of 10 did show disruption of liver functions as shown with the İSY test. It was emphasized that liver blood flow may influence indirectly liver function tests.

Table 4. Intergroup Hemodynamic Data

Variable	Group K (n = 20)	Group P (n = 20)	*P*
Heart rate	84 ± 10	88 ± 9	.193
Systemic arterial pressure	116 ± 10	104 ± 7	.000
Diastolic arterial pressure	68 ± 7	66 ± 5	.050
Mean arterial pressure	84 ± 9	78 ± 5	.011
Central venous pressure	3.8 ± 2.6	6.1 ± 2.9	.016

Abbreviations: Group K, PEEP 0 mm Hg; Group P, PEEP 10 mm Hg; PEEP, positive end-expiratory pressure.
Values are mean ± standard deviation (SD).

There are contradictory results related to the change in liver blood flow at different PEEP levels. Berendes et al [10] and Träger et al [11] evaluated mixed venous and hepatic venous oxygen saturations in patients who have undergone abdominal surgery at 0, 10, and 15 cm H_2O PEEP and determined that at PEEP levels, cardiac flow, mixed venous and hepatic venous oxygen saturation decreased in parallel. Liver metabolism was disrupted at a PEEP of $\leq$10 cmH_2O pressure application levels, and more clinically important changes were present at a PEEP of 15 cm H_2O. This situation was explained as compensation of reduced portal blood flow with hepatic arterial blood flow, that is, an effect of the buffering power of the hepatic artery. In studies with fixed PEEP in liver donors, Nieman et al [12] performed first ISY measurements approximately 20 minutes after graft separation and then İSY measurements were repeated on postoperative days 3 and 5. Although AST and ALT peaked on the first postoperative day in routine liver tests, bilirubin reached peak level on day 3 and it took 30 days to return to normal with PT. Lei et al [13] showed similar changes in liver tests in liver transplant donors. In our study, we followed liver test results for 3 days. First, we observed a peak change in ALT and AST, an increase in bilirubin, and

Table 5. Average Values of Groups According to PDR and R15 Measurement Times

Parameter	T0	T1	T2	T3	T4
PDR					
Group K	32 ± 6.8	21.7 ± 6.2*	15.5 ± 4.6*	14.7 ± 4.8*	15.6 ± 5.3*
Group P	30 ± 6.4	20 ± 7.2*	14.5 ± 2.8*	13.1 ± 2.4*	15.5 ± 3.2*
R15					
Group K	1.1 ± 0.8	6.3 ± 7.6*	11.5 ± 6.7*	14 ± 10.1*	13.3 ± 11.4*
Group P	1.7 ± 1.9	9.1 ± 13.3*	12.3 ± 4.4*	14.8 ± 5.4*	10.8 ± 5.7*

Abbreviations: group K, PEEP 0 mm Hg; group P, PEEP 10 mm Hg; PDR, plasma disappearance rate.
Values are mean ± standard deviation (SD).
*Variation according to T0 ($P < .05$).

PT prolongation, in line with results from previous studies. However, because we have compared liver function primarily with ISY test, we did not have enough follow-up demonstrating that laboratory values are returning normal. Therefore, we evaluated intergroup routine liver tests at these measurement times in addition to using the ISY test.

Saner et al [14] found that different PEEP levels (0, 5, and 10 mm H_2O) on hemodynamics, CVP, and iliac vein pressure in liver transplant recipients; CVP values were found to be significantly higher at PEEP values of 5 and 10 cm H_2O compared with a PEEP of 0 cm H_2O. Pulmonary wedge pressures were found to be significantly high at a PEEP of 10 cm H_2O. We found no difference between groups for heart rate, although we did for CVP, systemic arterial pressure, and MAP. In a study of different PEEP values in patients undergoing liver resection, Sand et al [15] found no difference in heart rate; however, cardiac flow was found to be significantly low at a PEEP of 10 cm H_2O and central and hepatic venous pressured were found to be significantly higher in heads up and heads down positions, compared with a supine position [15]. In the 2 studies performed by Saner et al [16] in liver transplant recipients, they found a significant difference at a PEEP of 15 cm H_2O in CVP, mean pulmonary arterial pressure, and pulmonary arterial wedge pressure. In our study, we found a significant difference between systemic arterial pressure and MAP (low in group P). However, we performed our study in completely healthy donors. In addition, decreases in MAP are compatible with previous studies.

Tralhao [17] examined how patients who have undergone liver hepatectomy owing to various reasons were affected by the Pringle maneuver; they did not specified the PEEP level used in the patients. However, they followed liver function tests with an ICG clearance test and passive liver tests, and did not find a significant difference compared with ICG-PDR and R15 measurements in patients groups in which the Pringle maneuver was used. These results are contrary to our study.

Although there were small changes in Hgb, Htc bleeding volume are compatible with increased CVP leading to PEEP level. This is more prominent in situations in which PEEP level is ≥15 cm H_2O. We conclude that evaluation of global liver function in elective liver donor patients and routine testing related to liver function are not affected by applied PEEP values between 0 and 10 cm H_2O.

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