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Does PEEP impair the hepatic outflow in patients following liver transplantation?

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Abstract *Objective:* Evaluation of the impact of end-expiratory pressure (PEEP) ventilation on venous liver outflow, portal vein, and hepatic artery flows as well as systemic hemodynamics in patients following liver transplantation (LT). *Design:* Prospective, interventional patient study. *Setting:* University hospital intensive care unit. *Patients:* 65 consecutive patients after LT *Interventions:* All patients were intubated and mechanically ventilated with biphasic positive airway pressure (BIPAP). The effects of three levels of PEEP (0, 5, and 10 mbar) applied at random order on hepatic inflow and outflow were studied in the immediate postoperative period. *Measurement and results:* Central venous-, arterial pressure, and cardiac index was recorded from every patient at three different PEEP levels (0, 5, and 10 mbar). Simultaneously, flow velocities in the hepatic-, portal vein, and hepatic artery were determined by Doppler ultrasound. PEEP of 10 mbar significantly increased central venous pressure in comparison with zero PEEP. Mean arterial pressure and cardiac index was not influenced. Hepatic inflow and outflow of the transplanted livers were not impaired by any of the used PEEP levels. *Conclusions:* BIPAP ventilation with PEEP levels up to 10 mbar does not affect systemic hemodynamics. Furthermore, neither venous outflow nor portal venous or hepatic artery inflow of the liver are impaired at PEEP levels up to 10 mbar immediately following liver transplantation. Although these results suggest that PEEP ventilation up to 10 mbar does not affect liver hemodynamics, further studies are needed to determine whether these findings could be confirmed for a longer ventilation period with PEEP.

Keywords Positive end-expiratory pressure · PEEP · Mechanical ventilation · Liver transplantation · Hepatic venous outflow · Color Doppler ultrasound

Introduction

Postoperative liver graft function in liver transplant patients is influenced by many factors, such as ischemia, infection, drug toxicity, and acute rejection. Furthermore, common postoperative intensive care interventions, such as application of vasoactive drugs [1] and mechanical ventilation with positive end expiratory pressure (PEEP) [2], might also affect graft function. Nasraway reported that liver graft performance depends on stable hemodynamics, sufficient organ blood flow, and especially on prevention of venous stasis of the liver [3]. The majority of studies investigating the effect of PEEP on systemic hemodynamic or splanchnic perfusion were performed in animal experimental settings [4, 5, 6]. The reported benefit of a higher PEEP-induced increase in lung volume in acute respiratory distress [7] may be marred by an associated increase in the thoracic pressure, which, in turn, could

impede venous return, thus altering systemic hemodynamics and hepatic venous outflow [8]. Alterations in the liver parenchyma may impair the compliance of the hepatic vein walls and might impair the hepatic outflow, as previously shown [9]. The entire splanchnic outflow (30–40% of the total venous return) must pass through the portal-sinusoidal pathway in the liver before returning to the right heart. In animal experiments, portal vein flow velocity and hepatic arterial blood flow velocity have been reported to decrease with PEEP, as a result of a simple increase of the downstream pressure [10]. However, to the best of our knowledge, the effect of PEEP on circulation and liver in- and outflow in patients with liver transplantation (LT) has not been analyzed; thus, we decided to investigate the relationship between PEEP, systemic hemodynamics, and flow velocities of the portal vein, hepatic artery, and hepatic vein following LT. Preliminary results have been reported as a poster presentation at the International Anesthesia Research Society meeting [11].

Patients and methods

After approval of the study protocol by the local ethics committee, 65 LT patients in the time period from March 2004 to August 2005 were included into the study. All patients were recruited at the surgical ICU of the Department of General-, Visceral-, and Transplant Surgery at the University Clinic Essen. Written informed consent was obtained from each patient before surgery. All operations were performed using standard surgical techniques and the same anesthetic regimen was applied to all patients. The LT was performed on all recipients without a veno-venous bypass. After admission to the intensive care unit (ICU), patients were routinely ventilated with a biphasic positive airway pressure (BIPAP) mode (Evita 4 ventilator, Draeger, Luebeck, Germany) with a PEEP of 5 mbar. The BIPAP is a pressure-controlled ventilation which allows spontaneous breathing at both pressure levels. The difference between the high- and low-pressure plateau provides patient's inspiration and expiration for controlled ventilation [12, 13]. Tidal volume (6–8 ml/kg ideal body weight), respiratory rate, and inspiratory oxygen fraction (FiO_2) were adjusted to maintain regular carbon dioxide levels (pCO_2 = 35–45 mmHg) and arterial oxygen saturation above 95%.

The study period for each patient was within the first 4 h after ICU admission. Only patients in deep general anesthesia without spontaneous breathing, but with stable hemodynamics, were included in the study, as we felt that it would be unethical to change PEEP levels in patients with gas exchange problems in such a critical phase following liver transplantation.

Patients who required PEEP levels higher than 5 mbar to achieve oxygen saturation $> 95\%$ or who needed norepinephrine treatment over 0.5 $\mu g/kg\,min^{-1}$ or inotropic support (dobutamine or epinephrine) were excluded from the study. During the study period no nursing maneuver, change of norepinephrine dose, volume replacement, or blood transfusion took place. The PEEP levels of 0, 5, and 10 mbar were randomly chosen. All hemodynamic and ultrasound color Doppler (USCD) data were simultaneously obtained from each patient at all three PEEP levels. Mechanical ventilation with a set PEEP was kept constant for at least 30 min prior to measurements in order to provide a steady state level for each measurement.

Doppler measurements may be difficult to obtain accurately. Iwao [14] stated that the intra-observer intraclass correlation coefficient was 0.77 for PV and 0.84 for superior mesenteric artery blood flow velocity, suggesting a good reproducibility; however, the inter-observer intraclass correlation coefficient was calculated to be 0.49 for PV and 0.57 for the superior mesenteric artery. In order to decrease the inter-individual variation of measurement, all Doppler measurements were performed by the same investigator. The measurements followed strict rules. The Doppler angle was $< 50°$ for all examinations. The velocities of the HA and PV were obtained in the liver hilum, whereas the flow velocities for HV were recorded in the middle hepatic vein (MHV), 1 cm from the orifice of the inferior vena cava.

The studies were performed using sonographic equipment with color Doppler capability (Siemens Sonoline, Erlangen, Germany) and a 3.5-MHz transducer. Doppler examinations were used to study the blood flow velocities in the portal vein (PV), the hepatic artery (HA), and the hepatic vein (HV). A normal HA Doppler waveform typically shows a rapid systolic upstroke with a continuous diastolic flow (see Fig. 1a) [15]. The HA systolic and diastolic flow velocities were recorded and resistive index (RI) was calculated using the following formula [16]:

RI = (peak systolic velocity – peak diastolic velocity) / peak systolic velocity.

Normal RI in the immediate postoperative period in adult liver transplant recipients is considered to be in the range between 0.45 and 0.8 [17]. An impediment of the liver outflow will normally increase the RI.

In healthy adults, the PV flow velocity has been described as being continuously hepatopetal with pulsatility variations caused by the respiration and cardiac cycle (see Fig. 1b) [18]. A decrease in PV flow velocity of less than one-third of the amplitude during systole seems to be physiological, as already demonstrated in healthy volunteers [18]. This pulsatility can be described by the peak and minimum portal vein flow velocities [19]. The waveform of the hepatic vein in healthy spontaneous breathing subjects can be described as triphasic (see Fig. 1c) [20]. To simplify the evaluation of hepatic venous blood velocity

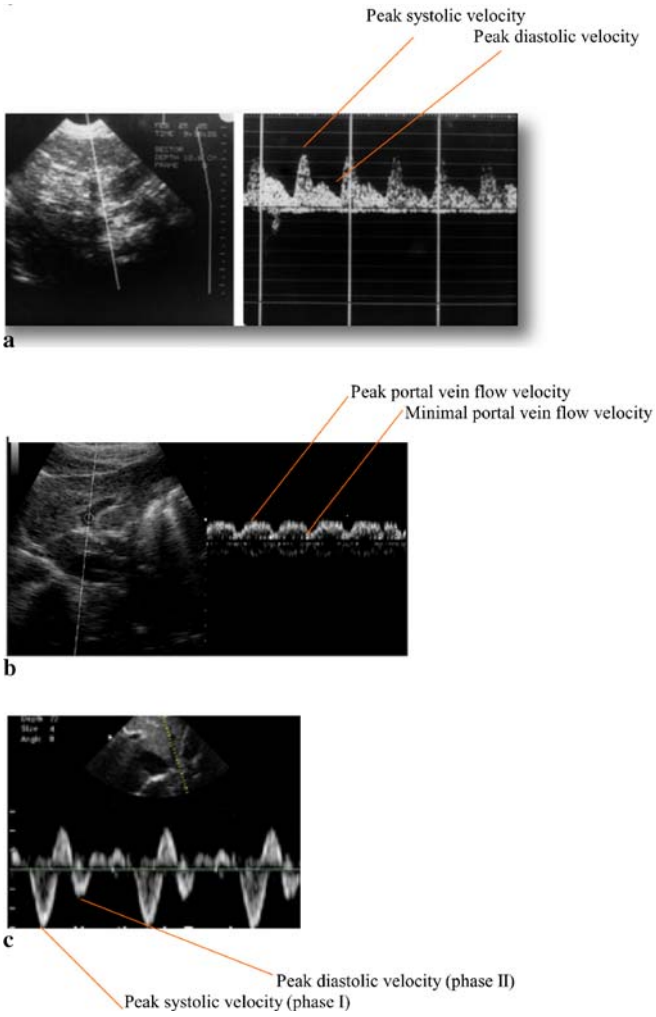

Fig. 1 **a** Flow pattern of the hepatic artery. The RI is calculated as: RI = (peak systolic velocity – peak diastolic velocity)/peak systolic velocity. **b** Flow pattern of the portal vein. **c** The waveform of the hepatic vein can be described as triphasic (To simplify the evaluation of hepatic venous blood velocity curves, two phases are defined.) Phase I (S wave) is a forward flow and correlates to systole; phase II (D wave) is another forward flow which correlates to diastole

curves, two phases are defined: phase I (S wave) is a forward flow and correlates to systole; phase II (D-wave) is another forward flow which correlates to diastole [20]. The systolic-diastolic (S/D) ratio is calculated as:

S/D = Maximum systolic velocity [cm/sec] / Maximum diastolic velocity (cm/s).

Mean systemic arterial pressure (MAP) and central venous pressure (CVP) were recorded using standard disposable pressure transducers (Medex Medical, Klein-Winternheim, Germany), together with leads II and V_5 of the electrocardiogram for the detection of heart rate (Sirecust 1281, Siemens, Erlangen, Germany). Cardiac output was measured by a thermodilution method, using the Stewart-Hamilton equation [21]. The cardiac index (CI) was calculated by dividing the cardiac output with body surface area (BSA). Arterial blood samples were used to determine pO_2, pCO_2, pH (Radiometer, Copenhagen), as well as hemoglobin amount and its saturation. To minimize any artificial changes in the hemodynamic variables during the measurements, pharmacological and volume therapy remained unchanged and no nursing maneuvers were performed during the measurement.

Statistical analysis

Categorical variables were analyzed by chi-squared test with Yates correction. Continuous variables were analyzed by one-way analysis of variance and *t*-test, when normal distribution was given. Non-normally distributed continuous variables were analyzed by the Kruskal-Wallis one-way analysis of variance on ranks.

The Mann–Whitney rank-sum test was performed when equal variance test failed. A value of $p < 0.05$ was considered significant.

Results

The most common diagnoses leading to liver transplantation were alcoholic cirrhosis (14 patients), hepatitis B and C cirrhosis (12 and 11 patients, respectively), acute liver failure (9 patients), and primary sclerotizing cholangitis (8 patients). The median body temperature was 36.2 °C (range 34.6–38.0 °C). Patient characteristics, demographic data, and relevant surgical data are given in Table 1.

During the study period 2 patients who required norepinephrine doses $> 0.5\,\mu g/kg\,min^{-1}$, as well as one patient who needed a PEEP of 10 mbar for sufficient oxygenation, were excluded from the study. None of the

Table 1 Patient and surgery data ($n = 65$ patients)

Characteristic	Value
Age (years)	51 ± 17
Weight (kg)	76 ± 19
Male/female (*n*)	34/31
MELD	18 (2–46)
Cold ischemia time (minutes)	358 ± 216
Warm ischemia time (minutes)	33 ± 12
SAPS II score	34 (4–62)

SAPS II New Simplified Acute Physiology Score (from [34]) Characteristics are reported as numbers (patients' gender); mean ± SD (age, weight, cold ischemia time, and warm ischemia time) or mean and range (SAPS II score) or median and range (MELD)

Table 2 Hemodynamic parameters and flow velocities of PV, HV, HA, at PEEP levels of 0, 5, and 10 mbar. *HR* heart rate, *MAP* mean arterial pressure, *CI* cardiac index, *CVP* central venous pressure, *PV* portal vein, *HA* hepatic artery, *HV* hepatic vein, *RI* resistive index, *S/D* systolic diastolic ratio

		PEEP = 0 mbar	PEEP = 5 mbar	PEEP = 10 mbar
	HR	90 ± 21	91 ± 21	90 ± 19
	MAP (mmHg)	92 ± 18	89 ± 10	87 ± 14
	CVP (mmHg)	6 ± 4	8 ± 5*	8 ± 4*
	CI (l min^{-1} m^{-2})	5.1 ± 1.8	4.7 ± 1.6	4.8 ± 1.9
PV flow velocity	Peak (cm/s)	39.7 ± 18.4	38.4 ± 18.4	37.4 ± 13
	Minimal (cm/s)	31.0 ± 16.1	28.6 ± 10.6	29.3 ± 10.4
HA flow velocity	Systolic (cm/s)	34.3 ± 13.1	35.3 ± 12.4	33.0 ± 11.6
	Diastolic (cm/s)	15.3 ± 6.7	16.2 ± 7.6	15.3 ± 7.8
	RI	0.54 ± 0.1	0.54 ± 0.1	0.53 ± 0.1
HV flow velocity	Systolic (cm/s) (phase I)	26.7 ± 9.3	24.5 ± 8.6	26.6 ± 12.1
	Diastolic (cm/s) (phase II)	17.5 ± 8.7	16.2 ± 6.7	17.7 ± 10.1
	S/D	1.7 ± 0.7	1.6 ± 0.4	1.6 ± 0.6

All data are listed as mean ± SD, * $p < 0.05$

enrolled patients received positive inotropic substances (dobutamine, dopamine, or epinephrine).

Influence of PEEP on the hepatic inflow

The mean blood flow velocity in the portal vein of the transplanted liver at zero PEEP (ZEEP) was 39.7 cm/s at the peak and 31.0 cm/s at the minimal flow level. We recorded no impact of PEEP on the PV flow velocity (Table 2).

The average systolic and diastolic blood flow velocities in HA were 34.4 and 15.3 cm/s, respectively. These values were also not influenced by increasing the PEEP to 5 and 10 mbar (Table 2). Consequently, the RI value remained stable at 0.5 for every PEEP level (Fig. 2).

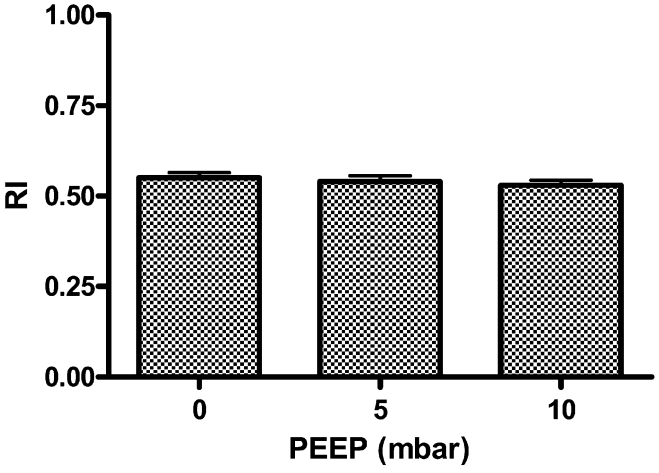

Fig. 2 Resistive index change with PEEP change. *RI* resistive index = (peak systolic-diastolic velocity)/peak systolic. The systolic and diastolic flow velocity of the hepatic artery remained nearly unchanged at each PEEP level. As a result, there is no impact of PEEP on the RI

Influence of PEEP on the hepatic outflow

The flow velocities in the hepatic vein were very similar at all PEEP levels studied; therefore, the S/D ratio remained unchanged at all three PEEP levels (Table 2).

Influence of PEEP on the central venous pressure, systemic arterial pressure, and cardiac index

As compared with ZEEP, CVP was increased by 24% at the PEEP level of 5 mbar (6 vs 8 mmHg; $p < 0.05$) and by 24% at the PEEP level of 10 mbar (6 vs 8 mmHg; $p < 0.05$). The mean arterial blood pressure (MAP), heart rate, and CI were not influenced by the mechanical ventilation with positive end-expiratory pressure (Table 2).

Discussion

The major finding of our study is that mechanical ventilation with positive end-expiratory pressure up to 10 mbar does not affect the liver outflow velocity. We found no significant changes of the hepatic vein flow velocities at any PEEP level. Our data are herewith in contrast to several studies of liver hemodynamics and invasive mechanical ventilation which demonstrated a negative effect of increasing PEEP values on the liver inflow and outflow [4, 8]. The basic conclusion from these studies was that a higher sinusoidal back pressure during a diaphragmatic descent results in a retrograde blood accumulation in the liver circulation, thus resulting in liver blood stasis and edema. In an animal model, Brienza [4] was able to show that an increase in PEEP correlates well with an increase in the right atrial pressure. The PEEP-induced diaphragm descent induced an increase of the liver venous resistance and a decrease of the hepatic vein flow.

Different modes of ventilation might have caused this difference between our and the aforementioned data. We

used a BIPAP mode of ventilation, whereas other investigators [4, 22, 23] used volume-controlled ventilation in their animal studies. Our data are compatible with the results from the study done by Krenn et al. [24]. They analyzed the effect of PEEP on the indocyanine green plasma disappearance rate (ICG_{PDR}) in LT patients, which is a dynamic test for liver performance. In their study, all patients were also mechanically ventilated in a BIPAP mode. They found no significant impact of PEEP on graft performance. Based on their data, they suggested that BIPAP mode might not influence hepatic outflow resistance and sinusoidal closing pressures as much as volume-controlled ventilation. Moreover, Kiefer et al. [25] investigated the effect of PEEP on splanchnic perfusion in acute lung injury. They concluded that PEEP itself does not have a consistent effect on the hepatico-splanchnic blood flow and metabolism, if the cardiac index remains stable. Our data are consistent with this observation as we have also found that PEEP levels up to 10 mbar do not significantly affect the cardiac index and at the same time the flow velocities of the liver vessels (HA, PV, HV) remain unchanged.

The hepatic vein flow curve in cirrhotic patients shows a characteristic lowering of the S/D ratio, sometimes even reaching a continuous flow [9]. This is most likely a consequence of pathological changes of the liver parenchyma, which may impair compliance of the hepatic vein walls. These rigid hepatic vein walls, in turn, may impair the hepatic blood outflow [9, 26]. Changed hepatic vein compliance and impaired liver outflow might be early indicators of an acute graft rejection [27]. Furthermore, Ko et al. [28] were able to show in living donor liver-transplanted (LDLT) patients that patients with a hepatic vein stenosis (and a consequent liver congestion) show a marked increase in the flow velocity and a switch to a monophasic flow in the hepatic veins.

We found no significant changes of the hepatic vein flow velocities at any PEEP level. The S/D ratio remained constant over the three different PEEP levels. Although we recorded an increased CVP, this did not affect hepatic vein flow velocity in our study. A PEEP might depress splanchnic perfusion and hepatic performance by depressing cardiac output, by increasing splanchnic vascular resistance, or by inducing venous stasis in the portocaval system. Bredenberg et al. [5] as a well as Matuschak et al. [8] demonstrated, in an animal model, that PEEP induced a reduction of cardiac output, which is accompanied by decreased hepatic blood flow; however, PEEP did not induce changes in the hepatic venous outflow if CI remained stable [7]. Volemic status of the patients can influence liver hemodynamics; however, since volume replacement (except for the continuous basal infusion) or blood transfusions were not allowed during the measurements at different PEEP levels, it is unlikely that a change in the volemic status of our patients influenced liver hemodynamics in our study.

In our study, portal vein flow remained nearly unchanged despite varying PEEP levels. The data of Someda [29] demonstrate a decreased portal flow velocity in liver-transplanted patients with portal veins stenosis. After successful treatment of the stenosis, flow velocity of the portal vein increased significantly. Our data may indicate that portal vein flow is independent of posthepatic venous pressure in LT patients, thus implying that denervated liver grafts are capable of compensating liver outflow impairment through some alternative mechanism(s). Åneman et al. [30] examined the effect of PEEP on splanchnic circulation and regional sympathetic outflow during PEEP ventilation in humans. They found that a decreased portal blood flow, increased mesenteric vascular resistance, and increased hepatic arterial flow observed during ventilation with a PEEP of 10 mbar occurred independent of sympathetic discharge. In our study, although no changes of flow velocities in liver vessels were observed, the unchanged MAP and heart rate at different PEEP levels make sympathic excitation by unloading of baroreceptors unlikely and therefore supports the results of Åneman et al. [30].

It was previously suggested that the RI index indicates hepatic artery patency [17, 31]. In our study, RI was not affected by increased PEEP, thus implying that hepatic artery patency was also not influenced by the BIPAP ventilation with a positive end-expiratory pressure.

The CVP significantly increased at PEEP of 5 and 10 mbar, as compared with ZEEP. As previously mentioned, Brienza et al. [4] were able to show that an increase of PEEP correlates well with an increase of the right atrial pressure in animals. Krenn and colleagues [24] analyzed the effects of PEEP on systemic hemodynamics in LT patients and found no effect of the PEEP on the CVP. In our patients, CVP increased significantly at a PEEP of 10 mbar. As we also observed that venous outflow from the transplanted livers was not impaired at any PEEP level studied, we conclude that a CVP up to 8 mmHg does not impair liver outflow.

Our study focused on the liver perfusion and systemic hemodynamics. We were not able to detect any subgroup of liver-transplanted patients with a more prominent negative effect of varying PEEP levels on any of the investigated parameters; however, it is plausible that a subgroup of liver-transplanted patients might be negatively influenced by increased PEEP levels. For instance, De Backer et al. [32] showed a covariance between oxygen delivery (DO_2) and oxygen consumption (VO_2) in the livers of septic patients as well as following dobutamine challenge or PEEP level alteration. Certainly, it would be of interest to analyze oxygen delivery and consumption in liver transplanted patients in order to assess whether a change in PEEP levels can affect transplanted livers in the same fashion as reported by De Backer et al. [32]; however, we do not routinely place liver vein catheters in patients who undergo liver transplantation, so that we were not able to analyze such changes and thus were not able to exclude the possibility that a subgroup

of liver-transplanted patients could be affected differently by PEEP changes than the majority of the LT patients.

Like any clinical trial, our study has some limitations. First of all, we investigated recipients with a normal lung function and did not apply PEEP levels higher than 10 mbar to avoid unnecessary lung overdistension. Reperfusion of the transplanted liver during the transplant operation could be associated with a brief but severe lung injury [33]. These patients might require a ventilation with a higher PEEP for a short period of time. Whether our data might be representative for these circumstances is a matter of speculation. Furthermore, the effect of mechanical ventilation with a PEEP over a prolonged period of time is also not clear.

Based on our study, however, we conclude that a short-term ventilation with PEEP levels up to 10 mbar in LT patients does not impair the in- and outflow velocities of the liver. Although further studies are necessary to ascertain that a prolonged mechanical ventilation with PEEP does not have a detrimental effect on the liver transplants, our study suggests that, in liver-transplanted patients with an acute lung injury, a short-term PEEP ventilation with up to 10 mbar should not be avoided.

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