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Original article

Splanchnic ischemia during mechanical ventilation

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SUMMARY

Background-aim: Positive end-expiratory pressure (PEEP) has been advocated as a prophylactic and therapeutic modality since it improves oxygenation and reopens atelectatic lung injury units. Thus, it is usually added to conventional mechanical ventilation in order to avoid development of post-operation atelectasis. However, high PEEP is known to result in diminished cardiac output, decreased venous return and transient ischemia to the abdominal viscera. On the other hand, prolonged gut hypoperfusion of different origin may cause mucosal barrier failure, which is considered an important factor for the initiation and/or perpetuation of bacterial translocation, leading, theoretically in humans, to sepsis. Considering that low PEEP may also lead to splanchnic hypoperfusion, we assessed the intestinal and hepatic hemodynamic in two step PEEP ventilation. Methods: The hepatic artery, portal vein, and superior mesenteric artery blood flow as well as the hepatic and intestinal mucosal microcirculation, the hepatic tissue pO_2 and the intestinal mucosal pH were assessed before and after 5 and 10 cmH_2O PEEP ventilation, in ten domestic pigs. Results: Statistical analysis revealed a significant decrease (p=0.0001) in all parameters during 5 cmH_2O and 10 cmH_2O PEEP ventilation period in compare to baseline. Hepatic artery exhibited a 20% reduction in 5 cmH_2O PEEP and a further 15% in 10 cmH_2O PEEP. Similarly, reductions of 11% and 9% in portal vein, of 15% and 11% in superior mesenteric artery, of 16% and 8% in hepatic microcirculation, and of 29% and 22% in intestinal microcirculation were noticed respectively, while hepatic parenchymal pO_2 reached 46% and intestinal mucosa pH fall to 7.29. Conclusion: These findings demonstrate that PEEP administration results to the impairment of splanchnic tissue perfusion.

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INTRODUCTION

Although positive end-expiratory pressure (PEEP) ventilation reopens atelectatic lung injury units, by increasing functional residual capacity, and improves arterial oxygenation however, it can, adversely, affect systemic hemodynamics by reducing venous return and cardiac output (CO) leading to transient ischemia in abdominal viscera.[1-4] Experimental studies suggested that mechanical ventilation with considerably high PEEP levels can lead to splanchnic hypoperfusion and marked decrease in hepatic, portal venous and mesenteric blood flow, despite only moderate decrease in cardiac output.[1,2,4] However, the results are still controversial as these effects are proportional to the PEEP level used.[1-7]

On the other hand, prolonged gut hypoperfusion of different origin impairs gastrointestinal tract barrier function, and triggers a generalized and uncontrolled inflammatory response which is considered as an important factor for the initiation and/or perpetuation of bacterial translocation. The last is reported to contribute, theoretically in humans, in the development of multiple organ failure and/or sepsis.[8-10]

Thus, the aim of the present study is the assessment of splanchnic tissue perfusion after PEEP application at the levels of 5 and 10 cmH_2O commonly used in operation theatres and ICU units.

MATERIALS AND METHODS

Animals

Ten male swine weighting 18-22kg were included in the study. The experimental protocol used was approved

by the Department of Animal Care and Use Committee of the Greek Ministry of Agriculture and adhered to the European Community Guiding Principles for the Care and Use of Animals.

Anaesthesia

After a 12-hour fasting period, anaesthesia was induced by 2ml Thalamonal [Janssen Cilag, Breese, Belgium] and 10mg Dormicum [Hoffmann-La Roche, Basle, Switzerland] given intramuscularly as premedication, followed, 20min later, by 7mg/kg of Pentothal [Abbott Lab, Alimos, Greece], then 1-2mg/kg Dormicum and 0.4mg/kg Norcuron [Organon, Teknika, Boxter, Holland]. A tracheostomy was performed and the animals were connected to a volume control ventilator, employing FIO_2:1. The ventilator was set to a tidal volume of 15ml/kg, with respiratory frequency adjusted to result a $PaCO_2$ of 35 to 40mmHg at the beginning of each experiment. The tidal volume was kept constant throughout the experiment while the respiratory rate was adjusted to maintain normocapnia. Anaesthesia was maintained by continuous infusion of 0.6mg/kg/h Norcuron and 1-2mh/kg/h Dormicum; Ringer's lactate was given at a rate of 8ml/kg/h, throughout the whole study period. Core temperature was kept at 37–39°C using heating blankets.

Cardiovascular and pulmonary hemodynamics

The carotid artery and external jugular vein were exposed through a right-sided neck dissection. Systemic arterial pressure was continuously monitored by a fluid-filled catheter with its tip in the proximal aorta. A 7-F Opticath Oximetric pulmonary artery catheter [Abbott Labs, Chicago, IL, USA] was inserted via the right external jugular vein and advanced distally into pulmonary artery for measurements of cardiac output (CO) and core body temperature. Cardiac output was measured by thermodilution method and the cardiac index was calculated by the mean of three cardiac output measurements, using 10ml of sodium chloride 0.9% solution at room temperature.

A complete hemodynamic profile was performed at each observation point, including mean arterial pressure (MAP), central venous pressure (CVP), pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure (PCWP). All variables were monitored continuously and recorded. The measurements were conducted at the expiratory phase and expressed in mmHg. A three lead ECG was used for monitoring of heart rate (HR).

For the determination of blood gas variables, arterial and mixed venous blood samples were drawn simultaneously in heparinized syringes and analysed immediately. Hematocrit level was measured in each phase, as well.

Hepatic and intestinal hemodynamics

A midline laparotomy was performed with the animal being in the supine position. The portal vein was isolated at the level of hepato-duodenal ligament, taking care not to damage the perivascular neural plexus. The gastroduodenal artery was ligated and common hepatic artery and the proximal part of the superior mesenteric artery were dissected free. Transit-time flow probes (8R, 4R and 4RB Transonic Systems Ithaca, NY, USA) were then placed around the vessels for continuous measurements of blood flow, (in ml/min) by means of the Transonics T101M flowmeter.

Intestinal mucosal and hepatic tissue microcirculation measurements were carried out using laser-Doppler single fiber probes connected to a laser Doppler flow meter. The probe used was PF319, 0,5 mm in diameter and 300 mm in length which was advanced approximately 2 cm deep in hepatic parenchyma (right lobe), through a needle which had been inserted percutaneously. Another fiber was positioned through a 22-gauge Abocath penetrating the jejunal wall, in optical contact with intestinal mucosa.

Data collection: According to this technique, blood flow is expressed in arbitrary perfusion units (PU), and is described as being equivalent to the number of red blood cells contained in the volume of blood through which the laser light is passing and at the speed at which these cells are moving. Thus, recording of the microvascular signals, was performed with a sampling frequency of 16 kHz (1 sample/0.06s) and a display frequency of 1 Hz. The flowmeter used (PeriFlux PF2B, Perimed Jarfalla, Sweden) was connected to a multichannel data acquisition system, combining an A/D converted (DT2801 series, DATA Translation, Marlboro, MA, USA) with a precision of 12 bits. Two monopolar channels were used: one for the microcirculation of the liver and one for that of the intestine. Three additional channels were used for the hepatic artery, portal vein and superior mesenteric artery flow recordings, while a suitable software programme, Perisoft (Perimed), was installed in an IBM PS2 computer, to store and analyze all the data. Data were extracted from this system as mean values established during registration sequences of 30 s.

A Clark-type electrode (Tissutrack, Pfizer Biomedical Sensors, High Wycombe, Bucks, UK) was advanced into the liver parenchyma for continuous tissue pO_2 monitoring.

Finally, a sigmoid tonometer (Tonometrics, Besthesda MD, USA) was inserted into the intestinal lumen through a small incision in the antimesenteric border for gut mucosal pH measurements at 30 min intervals.

The abdominal incision then was closed tightly in layers and the animals were allowed to recover from surgical stress for a 30 min period.

Study design

At the end of this stabilization period, baseline measurements were taken from systemic, intestinal and hepatic hemodynamics (study period T0). Blood samples for blood gas analyses and oxygen saturation measurements were drawn from carotid artery catheter. Next, two levels of PEEP, 5 cmH_2O and 10 cmH_2O, were sequentially added to the expiratory limb of the ventilatory circuit. After 30 min of hemodynamic stabilization at each level, all set of measurements were repeated, these study periods being T1 and T2, and blood sampling were performed. The total duration of the study was 90 min.

Control animals were not subjected to PEEP ventilation but all systemic, intestinal and hepatic hemodynamic measurements were performed as in experimental study group. The animals were sacrificed by an i.v. bolus of potassium chloride overdose. The correct positions of all catheters were verified and flow probes were checked *in situ* for zero blood flow recordings.

Statistical analysis

The data of systemic hemodynamic measurements and blood gas analysis, expressed as mean ± standard deviation (SD) for each time period, were assessed by repeated-measure analysis of variance. The hepatic and intestinal measurements were initially expressed as percentages of the baseline value (T0) for each animal, except of values of intestinal pH which were expressed as raw numbers ± SD, then averaged (±SD) across the animals for each of the 3 separate 30-min study periods. The 3 time points of each variable were assessed by repeated-measure analysis of variance. The Dunner-t test and Fisher's test were applied to determine a difference if a significant F value was obtained. Data from the control group were assessed separately by means of the same statistical methods and no comparison betweens the control and the study group animals were performed. All calculations were performed on a Macintosh PC, with the Statview (Brain Power, Calabalas, CA, USA) statistical package. A probability value of less than 0.05 was considered to be significant.

RESULTS

The systemic, intestinal and hepatic hemodynamic data obtained from the controls did not differ significantly throughout the 90-min study period remaining similar to the baseline measurements (T0) in the experimental study group. These findings confirm no intervention of anesthesia, ventilation, or cannulation and visceral manipulation on the hemodynamic profile of the animals, and thereafter the control group was no longer required.

Effects of PEEP on systemic hemodynamics

Systemic hemodynamic data are shown on table 1. In comparison with the T0 no significant changes in MAP and HR were seen. However, there was a significant decrease in CO at T1 and T2. CO dropped significantly for each PEEP level from a basal value of 4.33±1.09 to 3.56± 0.98 [$p<0.05$] and 2.86±0.99 [$p<0.05$] l/min for PEEP 5 and 10 cmH_2O, respectively. CVP was decreased also in

Table 1. Systemic hemodynamics (n=10)

Mean arterial pressure (mmHg)	118.5±24	113.6±20	117.0±17
Arterial pressure, systolic	161.2±41	145.8±38	154.8±35
Arterial pressure, diastolic	97.1±17	97.5±13	99.1±7.6
Heart rate (beats/min)	123±18	129±10	117±20
Cardiac output (l/min)	4.33±1.09	3.56± 0.98*	2.86±0.99*
Central venous pressure (cmH2O)	8.25±3.4	6.20±4.2	12.13±9.5+
Mean pulmonary artery pressure (mmHg)	20.75±5.8	24.50±5.1*	25.00±1.9*
Pulmonary artery pressure, systolic	42.25±10	50.6±10	50.0±3.5
Pulmonary artery pressure, diastolic	10±3.6	11.4±3.1	12.5±1.2
Pulmonary artery wedge pressure (mmHg)	5.50±1.6	6.45±3.7	8.62±3.8*

*Study periods: T0: baseline, T1: 30 min 5cmH_2O PEEP ventilation, T2: 30 min 10cmH_2O PEEP ventilation. P<0,05, * in relation to T0, $^+$ in relation to T1*

the two step PEEP ventilation but only at T2 point showed significance.

In the contrary, an increase in mean pulmonary artery pressure was noticed. Specifically, it was raised from 20.75±5.8 in basal line to 24.50±5.1 [p<0.05] in T1 and to 25.00±1.9 [p<0.05] mmHg in T2. Similarly, increase in pulmonary capillary wedge pressure was seen, but only at T2 point showed significance [mmHg].

Effects of PEEP on portal vein, hepatic and superior mesenteric artery blood flow and liver and intestinal mucosa microcirculation

Statistical analysis of the hepatic and intestinal measurements revealed a significant decrease [p=0.0001] in all parameters during the 5 (T1) and 10 cmH_2O PEEP (T2) ventilation period in relation to the baseline (T0) (table 2, fig. 1). Since these measurements expressed as percentages of the baseline value, it was found that hepatic artery exhibited a 20% reduction in 5 cmH_2O PEEP and a further 15% in 10 cmH_2O PEEP. Similarly, reductions of 11% and 9% in portal vein and of 15% and 11% in superior mesenteric artery were noticed.

The application of PEEP resulted in immediate significant changes [p<0.0001] in hepatic and intestinal microcirculation, as well (fig.2). In particular, hepatic microcirculation exhibited a 16% in 5 cmH_2O PEEP and a further 8%, in 10 cmH_2O PEEP. Similarly, reductions in intestinal microcirculation of 29% and 22% were seen in the two step ventilation, respectively.

Effects of PEEP on hepatic tissue pO_2 and intestinal pH

Each of the PEEP levels provoked a drop in liver oximetric values immediately after application which were statistically significant (p<0,0001) (fig. 3). Particularly, hepatic tissue pO_2 reduction was 20% from the baseline after 5 cmH_2O PEEP application and finally reached 46% in 10 cmH_2O PEEP.

A significant difference was found between intestinal mucosa pH values at baseline and T1 phase (7.41 vs 7.32) (fig.4). However, a further fall (7.29), but not statistically significant, was noticed also in T2. This reduction represents an important indication of hypoperfusion of as a value of less than 7.34 was considered as acidosis consequent to inadequate mucosa**l** oxygenation

DISCUSSION

Optimal PEEP level is considered that at which PaO_2 is maximal for a given FiO_2 or that set 2±3 cmH_2O above the lower inflection point of the pressure volume curve. Others regard as optimal the PEEP level at which compliance is maximal and the maximal DO_2 is achieved[11-12]. However, in clinical practice, PEEP level is usually increased until arterial oxygen saturation is greater than 90% or arterial oxygen tension exceeds an arbitrary level that is judged to be adequate while the patient is on an inspired oxygen content that is not toxic (usually FIO_2 less than or equal to 0.60). At the same time, PEEP ventilation is character-

Table 2. Abdominal organ hemodynamics (n=10)

			T0	T1	T2	P
	Hepatic artery		100.37	80.60*	65,53+	*P=0,0001 +P=0,001
Blood flow	portal vein		99,87	88,58*	79,94+	*P=0,0001 +P=0,0001
	superior mesenteric artery		102,75	87,16*	76,20+	*P=0,0001 +P=0,0001
Microcirculation		Liver	100	84,61*	76,31+	*P=0,0001 +P=0,0001
		Intestine	100,12	76,72*	54,76+	*P=0,0001 +P=0,0001
Hepatic tissue pO_2 (mmHg)			99,87	80,70*	54,95+	*P=0,0001 +P=0,0001
Intestinal mucosa pH			7,41	7,32*	7,29+	*P=0,001 +NS

*Study periods: T0: baseline, T1: 30 min 5cmH_2O PEEP ventilation, T2: 30 min 10cmH_2O PEEP ventilation. P<0,05, * in relation to T0, + in relation to T1, NS: not significant.*

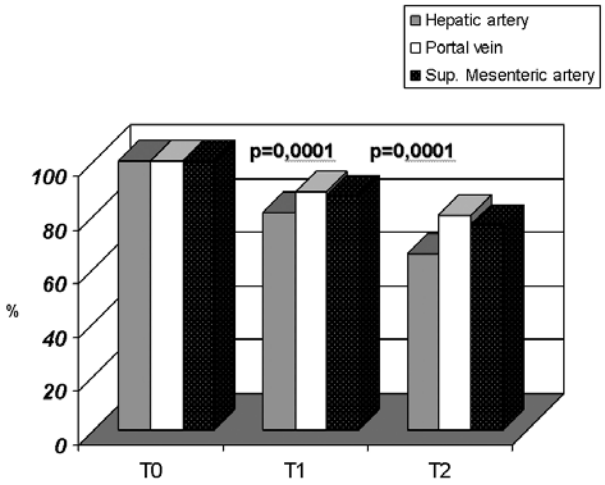

Fig. 1. Hepatic artery, portal vein and superior mesenteric artery blood flow.
Study periods: T0: baseline, T1: 30 min 5cmH_2O PEEP ventilation, T2: 30 min 10cmH_2O PEEP ventilation. P<0,05. All measurements were initially expressed as percentages of the baseline value (T0). Hepatic artery exhibited a 20% reduction in 5 cmH_2O PEEP and a further 15% in 10 cmH_2O PEEP. Portal vein and superior mesenteric artery reductions were 11% and 9% and 15% and 11%, respectively.

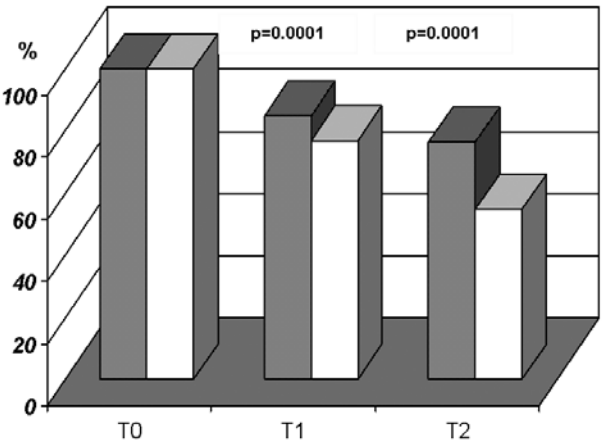

Fig. 2. Liver and intestinal mucosal microcirculation
Study periods: T0: baseline, T1: 30 min 5cmH_2O PEEP ventilation, T2: 30 min 10cmH_2O PEEP ventilation. P<0,05. All measurements were initially expressed as percentages of the baseline value (T0). Hepatic microcirculation exhibited a 16% in 5 cmH_2O PEEP and a further 8%, in 10 cmH_2O PEEP. Similarly, reductions in intestinal microcirculation of 29% and 22% were seen in the two step ventilation, respectively.

ized by unfavourable effects such as increase in intrathoracic, intra-alveolar pressure and subsequent rise in pulmonary vascular resistance as well as an increase in CVP

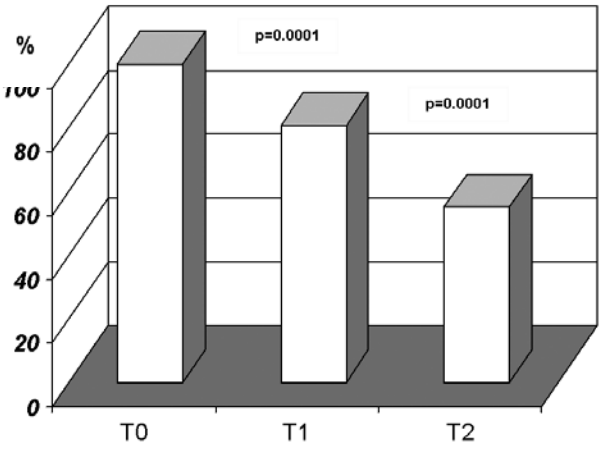

Fig. 3. Hepatic tissue pO_2
Study periods: T0: baseline, T1: 30 min 5cmH_2O PEEP ventilation, T2: 30 min 10cmH_2O PEEP ventilation. P<0,05. All measurements were initially expressed as percentages of the baseline value (T0). Hepatic tissue pO_2 exhibited a 20% reduction in 5 cmH_2O PEEP which reached 46% in 10 cmH_2O PEEP.

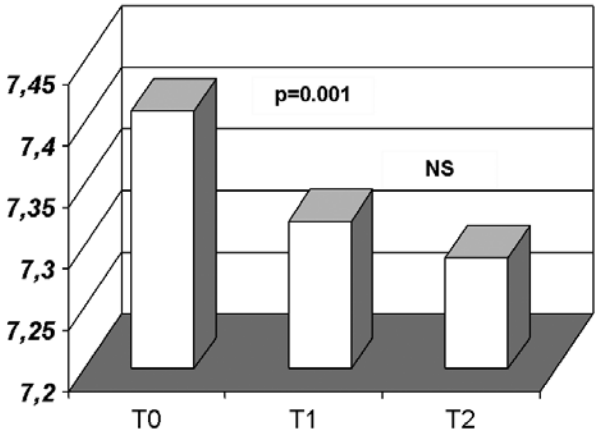

Fig. 4. Intestinal mucosa pH
Study periods: T0: baseline, T1: 30 min 5cmH2O PEEP ventilation, T2: 30 min 10cmH2O PEEP ventilation. P<0,05. A significant difference was found between intestinal mucosa pH values at baseline and T1 phase (7.41 vs 7.32). However, a further fall (7.29), but not statistically significant, was noticed also in T2.

and portal venous pressure creating difficulties in venous return, which are well documented.[1,2,13] Additionally, several experimental studies[1-4] have reported extra pulmonary disturbances: marked and consistent reductions in CO and total splanchnic and portal venous blood flow in a dose-dependent manner; decrease hepatosplanchnic perfusion even at PEEP levels lower than 10 cmH_2O.[1,2,14,15]

Similarly, in the present study where 5 and 10 cmH_2O PEEP were used intestinal and hepatic perfusion was found

to be fully disturbed and splanchnic hypoxia became apparent. However, PEEP ventilation, even at a level as low as 5 cmH_2O being a pressure very common used in mechanically ventilated patients, do have impact on splanchnic perfusion.

These effects in CO and local splanchnic circulation, at different levels of PEEP are still controversial.[15-17] Thus, in order to explain the redistribution of blood flow in abdominal viscera after PEEP application, several physical, humoral, and neural mediation possible mechanisms are considered to be implicated. Pizov et al[18] reported that incremental PEEP, when applied in normovolemic subjects without lung injury, causes a gradual decrease in CO. As the most accepted explanation for that effect is considered a reduction of preload, due to reduced venous return, since there is excessive increase in intrathoracic pressure at the presence of preserved cardiac contractility.[19,20] The reduction in CO, consequently, promotes a redistribution of blood flow away from the splanchnic circulation when, especially, a relative hypovolaemia may exists. As alterations in splanchnic blood flow attributed to PEEP occur in parallel to those in CO, these effects are usually reversed by fluid administration.[3,21] In accordance, Akinci et al[22] demonstrated a lack of impact on splanchnic blood flow when PEEP is not accompanied by decreased CO, as it is showed in animal studies[2,3] and in human[17]. In our study, CO was 4.33±1.09 and when PEEP 5 and 10 cmH_2O added decreased significantly (3.56± 0.98 and 2.86±0.99, respectively). Similarly to the CO reduction, hepatic artery, portal vein and superior mesenteric artery blood flow exhibited a 20%, 11% and 15% reduction, respectively with a PEEP 5 cmH_2O and a further reduction of 15%, 9% and 11%, respectively, when PEEP added was of 10 cmH_2O. The hepatic and intestinal hypoperfusion was also corroborated by the parallel reduction in hepatic (16% and 8%) and intestinal (29% and 22%) microcirculation, respectively.

It is well known that extrahepatic mechanical and hemodynamic forces, associated with respiration, affect the liver even during spontaneous breathing. Moreno et al.[23] described a phasic inspiratory reduction in hepatic outflow, due to direct hepatic compression by the descending diaphragm, which increase transhepatic vascular resistance despite decreases in downstream caval pressure. The increased intra-abdominal pressure due to transmission of pressure from the thoracic cavity is considered to be the cause of the decrease in mesenteric blood flow (MBF) during PEEP ventilation. Brienza et al.[24] in a solatedi liver model showed that, at adequate filling volume, the decrease in liver blood flow is mainly determined by direct compression of the liver by diaphragmatic descent. Fessler et al.[25] and Takata and Robotham[26] also demonstrated that PEEP increases the intra-abdominal pressure around the abdominal vasculature. Therefore, it could be hypothesised that the pressure gradient for venous return is not reduced by PEEP, especially in patients with hypervolemia.[27]

On the other hand, as early as 1972 a 5-7 cmH_20 PEEP-induced reduction of portal venous flow during concomitant increases in portal pressure relative to atmosphere was considered responsible due to increases in intrahepatic vascular resistance.[28] As the law of Poiseuille states, flow is proportional to the gradient of pressure and is inversely proportional to resistance. PEEP is influential on both variables. The venous return compromise precipitated by the increased intrathoracic pressure raises the portal venous pressure (P2).[21] This in turn sets of a chain of intestinal autoregulation, involving increases in transmural pressure and arteriolar tone, and resulting in vasoconstriction.

However, Bredenberg and Paskanik[21] found that, during 10 and 15 cmH_20 PEEP, portal flow reductions have been reversed, after CO was returned to pre-PEEP levels by intravascular volume loading, as it is shown by others[3]. Although it cannot exclude the possibility that changes in diaphragm position may have direct mechanical effects on the liver during PEEP, combined increases in the common downstream outflow resistance and CO associated with intravascular volume expansion appear to override such potential effects on steady-state hepatic outflow. However the significant hepatic venous capacitance makes this explanation less likely.[29] Regardless intestinal perfusion, Love et al.[5] reported also that, although MBF and CO fell progressively as PEEP was increased in rats from 10- to 15- and to 20-cm H_2O pressure, however, MBF remained depressed despite normalization of CO whereas the abdomen was kept open and therefore was at ambient atmospheric pressure.

Humoral or neural mechanisms are thought to be responsible for MBF reduction since mediators including angiotensin, endothelin, and vasoconstricting eicosinoids are implicated.[31] In an acute lung injury model ventilated with 10 cmH_2O pressure PEEP decreased portal venous blood flow was reversed after dopamine injection.[30]

Lefrant at al.[32] reported in open and in closed abdomen animals, a decrease in hepatic artery blood flow without significant change in portal vein blood flow during PEEP, and without correlation with CO or $PaCO_2$ changes. The hepatic arterial buffer response can probably not explain

the marked decrease in hepatic artery blood flow, since there was a slight only increase in portal flow and only in open abdomen animals.

Other studies have shown splanchnic O_2 consumption to be maintained, even at high levels of PEEP, by a compensatory increase in O_2 extraction.[30,33] Winsö et al.[34] in a clinical study during PEEP ventilation, noticed a decreased portal blood flow, while splanchnic VO_2 was maintained probably due to a compensatory increase in splanchnic O_2 extraction. Aneman et al.[29] found mesenteric and hepatic O_2 consumption to remain stable after application of 10 cmH_2O PEEP, although mesenteric and hepatic O_2 delivery decreased. Similarly, in patients suffers acute respiratory failure PEEP did not significantly alter splanchnic blood flow and did not affect indices of tissue hypoxia such as gastric mucosal PCO_2 and the blood lactate to pyruvate ratio.[17] However, in the present study hepatic parenchymal pO_2 reduced from 99.87±4.93 at baseline to 80.70±9.08 and furthermore to 54.95±5.11 at T1 and T2 points which is statistically significant [p=0.0001].

In conclusion, although low and short-term application of PEEP by itself results to the impairment of splanchnic tissue perfusion it is conceivable that longer durations would have led to more prominent reductions and statistically significant differences. The maintenance of cardiac output during changes in PEEP should prevent potential impairment of splanchnic perfusion. Despite experimental evidence regarding the effects of PEEP on splanchnic perfusion however large studies in humans are lacking suggesting the need for further investigation.

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