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Deterioration of Visceral Perfusion Caused by Intra-Abdominal Hypertension in Pigs Ventilated with Positive End-Expiratory Pressure

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Abstract Experimental studies and clinical experience suggest that the combination of positive end-expiratory pressure (PEEP) ventilation and intra-abdominal hypertension might alter splanchnic hemodynamics to a significantly greater degree than the effect of either of them alone. Therefore, we assessed the intestinal and hepatic hemodynamics in two steps of PEEP ventilation, adding tense pneumoperitoneum in a pig model. The hepatic artery, portal vein, and superior mesenteric artery blood flow, as well as the hepatic and intestinal mucosal microcirculation, and the hepatic pO_2 and intestinal mucosal pH, were assessed before, then with 5 cmH_2O and 10 cmH_2O PEEP alone, and in combination with a 12-mmHg pneumoperitoneum, in ten domestic pigs. Statistical analysis of the hepatic and intestinal measurements revealed a significant decrease ($P = 0.001$) in all parameters in relation to the baseline, during the 5-cmH_2O and 10-mmH_2O PEEP ventilation period. The addition of 12 mmHg intra-abdominal pressure led to an extreme deterioration in all parameters ($P = 0.001$), in relation to both the baseline and the 10-cmH_2O PEEP measurement. These findings demonstrate that PEEP and intra-abdominal hypertension act cumulatively on the abdominal viscera, producing conditions of extremely low hypoperfusion and ischemia.

Key words Intra-abdominal pressure · Abdominal compartment syndrome · Positive end-expiratory pressure · Pneumoperitoneum

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Introduction

Recognition of the abdominal cavity as a compartment with the potential to cause life-threatening local and systemic manifestations has recently gained attention. In fact, abdominal compartment syndrome has been broadly defined as multiple organ dysfunction attributable to an increase in intra-abdominal pressure (IAP). In this hypertensive environment, all the intraperitoneal viscera is hypoperfused due to direct mechanical compression, resulting in splanchnic ischemia.[1]

The clinical significance of these effects of intra-abdominal hypertension is particularly relevant for patients who have suffered massive abdominal injury, and are being managed by damage control surgical techniques.[2] The majority of such patients, being at a high risk of abdominal compartment syndrome development, are treated in intensive care units and commonly ventilated with positive end-expiratory pressure [PEEP].

In general, PEEP is added to conventional mechanical ventilation in patients prone to the development of postoperative atelectasis. The application of low PEEP levels has been advocated as both a prophylactic and therapeutic modality, as it improves oxygenation and reopens atelectatic lung units. Moreover, PEEP might be especially advantageous to patients whose respiratory mechanism is compromised by an elevation in IAP, as this decreases diaphragmatic excursion, resulting in decreased end-expiratory tidal volume, which may in turn increase CO_2 retention.[3]

Studies on the effects of PEEP ventilation on regional vascular beds have yielded conflicting results; however, most of them strongly suggest a decrease in abdominal splanchnic perfusion, caused by a progressive decline in cardiac output, and subsequent abnormalities of its distribution.[4–6] These suggestions derived from experimental and clinical studies led us to suspect that the

development of IAP to an already PEEP-ventilated subject might alter splanchnic hemodynamics, significantly beyond the effect of PEEP or IAP alone.

Since the results of two experimental studies have already demonstrated that the combination of PEEP and elevated IAP markedly altered cardiopulmonary and hemodynamic performance,[7,8] we decided to investigate whether similar effects would be reproducible in the abdominal viscera. Thus, the purpose of this study was to assess the effects of tense pneumoperitoneum on the intestinal and hepatic hemodynamics in ventilated pigs subjected to a gradual increase in PEEP.

Materials and Methods

Animals and Anesthesia

These experiments were performed on ten domestic pigs weighing 18–22 kg, after a 12-h fasting period. As a control, four similar animals not subjected to either PEEP ventilation or IAP induction were examined. 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.

Anesthesia was induced with 2 ml Thalamonal (Janssen, Cilag, Beerse, Belgium) and 10 mg Dormicum (Hoffmann-La Roche, Basle, Switzerland) given intramuscularly (i.m.), as premedication followed 20 min later by 7 mg/kg Pentothal (Abbott Lab, Alimos, Greece), then 1–2 mg/kg Dormicum and 0.4 mg/kg Norcuron (Organon, Teknika, Boxtel, Holland). A tracheostomy was performed and each animal was connected to a volume-control ventilator, employing $FIO_2 = 1$. The ventilator was set to deliver a tidal volume of 15 ml/kg, with respiratory frequency adjusted so that the $PaCO_2$ was between 35 and 40 mmHg at the beginning of each experiment. The tidal volume was kept constant during the experiment and the respiratory rate was adjusted to maintain normocapnia. Anesthesia was maintained by a continuous infusion of 0.6 mg/kg Norcuron and 1–2 mg/kg Dormicum per hour, while lactate Ringer's solution was given at a rate of 8 ml/kg per hour, throughout the experiment.

Cardiovascular and Pulmonary Hemodynamics

The left femoral artery and vein were dissected via a femoral cut-down, and arterial and pulmonary artery catheters were inserted. A 7-F Opticath Oximetric pulmonary artery catheter (Abbott Labs, Chicago, IL, USA) was used for hemodynamic monitoring. A complete hemodynamic profile was performed at each observation point, and included mean arterial pressure (MAP), central venous pressure (CVP), pulmonary artery pressure (PAP), and pulmonary capillary wedge pressure (PCWP). All measurements were conducted at the expiratory phase and expressed in mmHg.

Cardiac output was measured by the thermodilution method and the cardiac index was calculated by the mean of three cardiac output measurements, using 10 ml of sodium chloride 0.9% solution at room temperature. For the determination of blood gas variables, arterial and mixed venous blood samples were drawn simultaneously in heparinized syringes and analyzed immediately.

Hepatic and Intestinal Hemodynamics

A midline abdominal incision was made and a 16-F balloon-tipped catheter was guided through the abdominal wall via a stab wound, and inserted into the urinary bladder to monitor urine output. The gastroduodenal artery was ligated. Taking care not to damage the perivascular neural plexus, transit-time flow probes (8R, 4R, and 4RB; Transonic System, Ithaca, NY, USA) were placed around the portal vein, the common hepatic artery, and the superior mesenteric artery, respectively, for blood flow assessment, expressed, in ml/min, through the Transonics T101M flowmeter.

Continuous monitoring of the intestinal mucosal and the hepatic parenchymal microcirculation was carried out using the laser-Doppler technique. A laser-Doppler optical single fiber (PF319), 0.5 mm in diameter and 300 mm in length, was advanced approximately 2 cm deep into the hepatic parenchyma, through a needle which had been inserted percutaneously. Another optical fiber was positioned through a 22-gauge Abocath, penetrating the jejunal wall in optical contact with the intestinal mucosa. Recording of the microvascular signals, expressed in relative units of flow, was performed with a sampling frequency of 16 Hz (1 sample/0.06 s) and a display frequency of 1 Hz. The flowmeter used (Periflux PF2B, Perimed, Järfälla, Sweden) was connected to a multichannel data acquisition system, combining an A/D converter (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 program, Perisoft (Perimed), was installed in an IBM PS2 computer, to store and analyze all the data. Hepatic tissue pO_2 monitoring was established by a Clark-type electrode (Tissutrack, Pfizer Biomedical Sensors, High Wycombe, Bucks, UK) which was advanced into the liver. Finally, a sigmoid tonometer (Tonometrics,

Bethesda MD, USA) was inserted into the intestinal lumen through a small incision in the antimesenteric border as a means of detecting gut ischemia, since a value of less than 7.34 is considered as acidosis consequent to inadequate mucosal oxygenation.

Intra-Abdominal Hypertension Induction

A Verres needle was inserted percutaneously into the abdominal cavity, after which the abdominal incision was closed in layers, and the exit points of the catheters and sensors were sealed using purse-string sutures. The Verres needle was connected to an insufflator (Wisap, Semm System, Sauerlach, Germany) and pneumoperitoneum was created using nonheated helium gas, at a constant pressure of 12 mmHg. Inert gas helium was chosen instead of CO_2, to avoid overestimation of the tonometer readings.

Experimental Protocol

After surgical preparation, the animals were allowed to stabilize for a 30-min period with no PEEP ventilation, and baseline measurements were then taken from systemic, intestinal, and hepatic hemodynamics, being study period T_0. Next, two levels of PEEP, at 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 sets of measurements were repeated, these study periods being T_1 and T_2. After termination of the T_2 measurement, while the animals were being ventilated at 10 cmH_2O PEEP, the intra-abdominal pressure was increased to 12 mmHg by gas insufflation and measurements were repeated after 30 min and 60 min, these study periods being T_3 and T_4. The animals were then killed by a KCl overdose.

The control animals were maintained under the same protocol of 150 min anesthesia, but were not subjected to PEEP ventilation or to an increase in intra-abdominal pressure. All systemic, intestinal, and hepatic hemodynamic measurements were performed as in the experimental study group.

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 analyses of variance. The hepatic and intestinal measurements were initially expressed as percentages of the baseline value (T_0) for each animal, except for values of intestinal pH which were expressed as raw numbers ± SD, then averaged (±SD) across the animals for each of the five separate 30-min study periods. The five time points for each variable were assessed by repeated-measure analysis of variance. The Dunnet *t*-test and Fisher's test were applied to determine differences 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 between the controls and the study-group animals was 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 150-min study period, remaining similar to the baseline measurements (T_0) in the experimental study group. These findings confirmed 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.

Statistical analysis performed on the main group of animals revealed that the systemic hemodynamic data deteriorated slightly during the progress of the experiment (Table 1). Statistical analysis of the hepatic and intestinal measurements revealed a significant decrease ($P = 0.001$) in all parameters during the 5 (T_1) and 10 cmH_2O PEEP (T_2) ventilation period in relation to the baseline (T_0), while the addition of 12 mmHg intra-abdominal pressure led to a further deterioration in all parameters ($P = 0.001$), in relation to both the baseline (T_0) and T_2 measurements (Figs. 1–7).

Discussion

The decade of the 1990s generated a large number of experimental and clinical studies to promote the notion that intra-abdominal hypertension, which can result in abdominal compartment syndrome, is a clinically significant entity in critically ill surgical and traumatized patients [9]. This syndrome has great relevance in the practice of surgery and the care of critically ill patients on multiple organ systems, because of the effects of elevated pressure within the confined space of the abdomen. On the other hand, the beneficial effects of PEEP ventilation for such patients, including improved oxygenation, increased functional residual capacity, and decreased intrapulmonary vascular shunting, have been established, although it is known that high levels of PEEP can result in diminished cardiac output,

Table 1. Systemic hemodynamics

	T_0	T_1	T_2	T_3	T_4
Mean arterial pressure (mmHg)	118.5 ± 24	113.6 ± 20	117.0 ± 17	111.1 ± 24	108.8 ± 22
Arterial pressure, systolic	161.2 ± 41	145.8 ± 38	154.8 ± 35	148.4 ± 41	140.8 ± 40
Arterial pressure, diastolic	97.1 ± 17	97.5 ± 13	99.1 ± 7.6	92.5 ± 16.9	92.5 ± 14.1
Heart rate (beats/min)	123 ± 18	129 ± 10	117 ± 20	135 ± 25†	134 ± 16†
Cardiac output (l/min)	4.33 ± 1.09	3.56 ± 0.98*	2.86 ± 0.99*	3.56 ± 1*†	3.50 ± 1.23*†
Central venous pressure (cmH_2O)	8.25 ± 3.4	6.20 ± 4.2	12.13 ± 9.5+	11.07 ± 4.6	10.27 ± 4.8
Pulmonary artery pressure (mmHg)	20.75 ± 5.8	24.50 ± 5.1*	25.00 ± 1.9*	28.25 ± 3.4*+	26.37 ± 2.2*
Pulmonary artery pressure, systolic	42.25 ± 10	50.6 ± 10	50.0 ± 3.5	56.5 ± 5	53.6 ± 2
Pulmonary artery pressure, diastolic	10 ± 3.6	11.4 ± 3.1	12.5 ± 1.2	14.1 ± 2.9	12.75 ± 2.5
Pulmonary artery wedged pressure (mmHg)	5.50 ± 1.6	6.45 ± 3.7	8.62 ± 3.8*	8.87 ± 4.0*	8.62 ± 3.5*

Study periods: T_0, baseline; T_1, 30 min of 5 cmH_2O PEEP ventilation; T_2, 30 min of 10 cmH_2O PEEP ventilation; T_3, 30 min of increased (12 mmHg) abdominal pressure plus 10 cmH_2O PEEP ventilation; T_4, 60 min of increased abdominal pressure plus 10 cmH_2O PEEP ventilation
$P < 0.05$: * in relation to baseline (T_0), + in relation to T_1, and † in relation to T_2

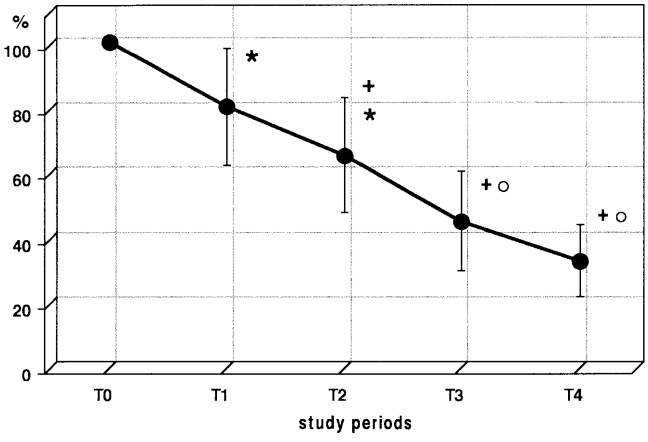

Fig. 1. Hepatic artery blood flow. Data from hepatic and intestinal measurements during the course of PEEP ventilation and increased abdominal pressure are analyzed in this and all subsequent figures. Values are expressed as mean ± SD for each time period. T_0–T_5 represent the study periods. T_0, baseline; T_1, 30 min of 5 cmH_2O PEEP ventilation; T_2, 30 min of 10 cmH_2O PEEP ventilation; T_3, 30 min of increased (12 mmHg) abdominal pressure plus 10 cmH_2O PEEP ventilation; T_4, 60 min of increased (12 mmHg) abdominal pressure plus 10 cmH_2O PEEP ventilation. *Star*, $P < 0.05$, in relation to the baseline T_0; *plus sign*, $P < 0.05$, in relation to T_1; *circle*, $P < 0.05$, in relation to T_2

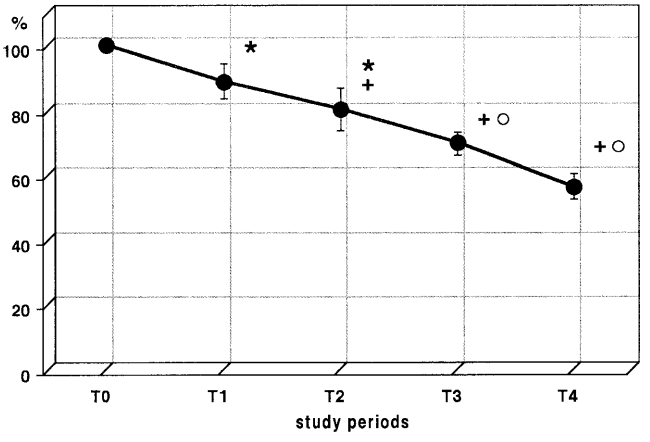

Fig. 2. Portal vein blood flow. For explanation, see Fig. 1

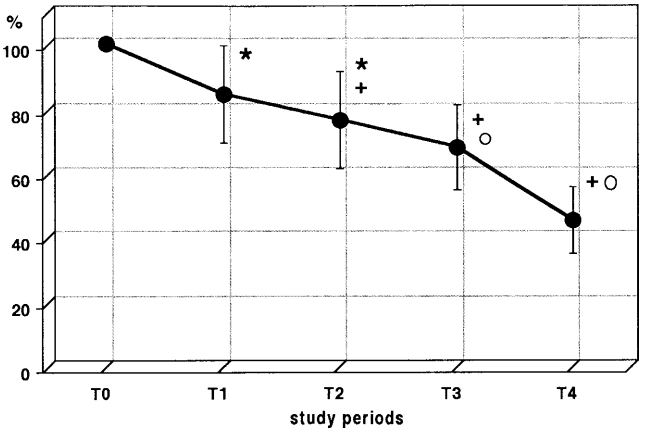

Fig. 3. Liver microcirculation. For explanation, see Fig. 1

decreased venous return, and transient ischemia to the abdominal viscera.[10–12]

The results of this study confirmed the negative influence of PEEP on splanchnic hemodynamics, even at a level as low as 5 cmH_2O, being a pressure very often used in mechanically ventilated patients. At the level of 10 cmH_2O of PEEP the intestinal and hepatic perfusion was found to be fully disturbed and splanchnic hypoxia became apparent. It is well known that the optimum level of PEEP is titrated using serial measurements of variables derived from cardiac output, and the level resulting in the highest DO_2 is said to be the optimum level. However, since the aim of PEEP is to prevent atelectasis occurring secondary to compression by the overlying lung, it should not exceed the hydrostatic pressure imposed on a region equivalent to the dorsal-

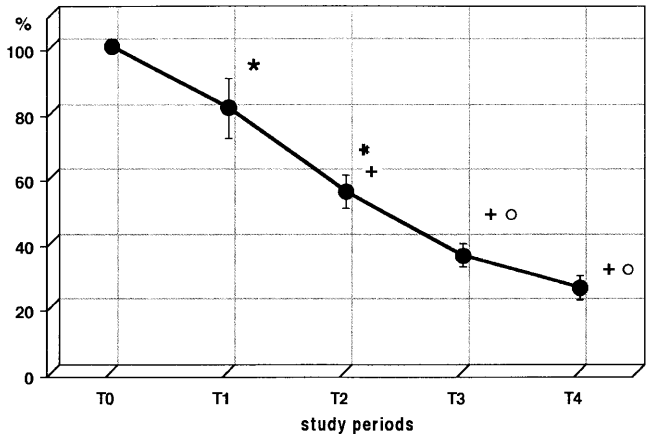

Fig. 4. Hepatic tissue pO_2. For explanation, see Fig. 1

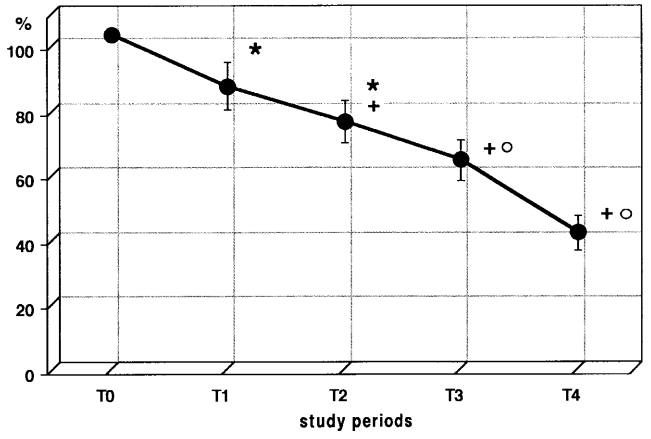

Fig. 5. Superior mesenteric artery blood flow. For explanation, see Fig. 1

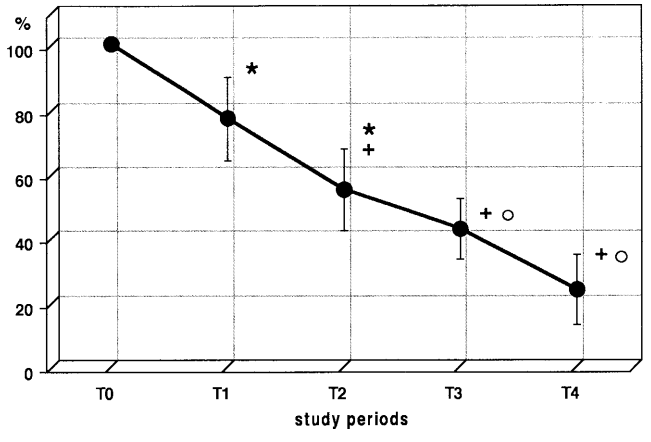

Fig. 6. Jejunal microcirculation. For explanation, see Fig. 1

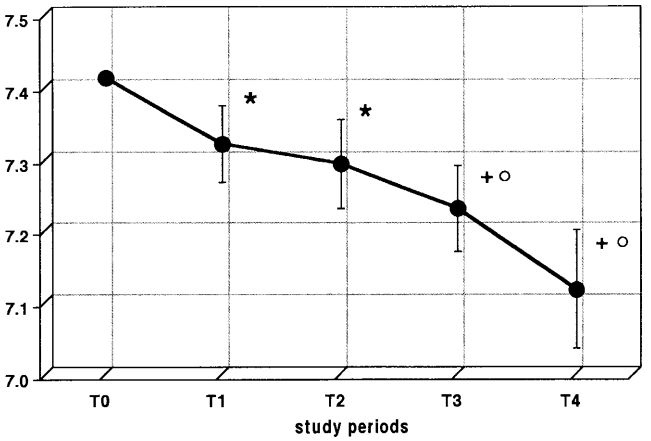

Fig. 7. Jejunal tissue pH. For explanation, see Fig. 1

ventral height of the lung in the supine subject. According to previous definitions, the accepted value of maximum PEEP pressure is 10–15 cmH_2O for the adult human male.[13] From this point of view, although the maximum level of PEEP applied in our animals, being 10 cmH_2O, could not be considered relevant to clinical practice, their splanchnic hemodynamics were found to be disturbed, even at lower levels of PEEP.

Even if it seems likely that PEEP ventilation adversely affects intra-abdominal hypertension in a critically ill patient who was suffered trauma, several questions remain unanswered, namely, what is the degree of "cooperation" between PEEP and IAP in the creation of an ischemic environment within the abdomen? Furthermore, since the critical level of IAP for the development of splanchnic ischemia is unknown, and as observations suggest that patients do not respond uniformly to the same level of IAP, are lower IAP levels needed for the development of splanchnic ischemia in a PEEP-ventilated patient? Despite the fact that all clinical studies dealing with abdominal compartment syndrome have reported that the majority of patients treated in intensive care units were mechanically ventilated, no study has described in detail the use of PEEP and the levels given. Therefore, it would be advisable if both clinical investigations and basic research on abdominal compartment syndrome took the influence of PEEP and intra-abdominal hypertension in the intraperitoneal viscera into consideration.

In our study, when 12 mmHg IAP was created in the animals being ventilated at 10 cmH_2O, a further reduction in their visceral blood flow and more severe hepatic and intestinal ischemia was revealed. More specifically, the intestinal bed had a 35% decrease in superior mesenteric artery blood flow and a 31% decrease in mucosal microcirculation, followed by an extremely low mucosal pH_i of 7.1. Moreover, in the hepatic bed, there

was a significant reduction in the total blood inflow, to 33% in the hepatic artery and 24% in the portal vein, as well as a 31% reduction in its microcirculation, and a 30% reduction in its parenchymal pO_2; all these percentages being expressed in relation to the T_2 measurement.

Recent data suggest that some of the adverse effects of elevated IAP occur at lower levels than previously described and appear before the development of fulminant abdominal compartment syndrome.[14] An IAP greater than 15 mmHg was found to impair intestinal perfusion at the mucosal and submucosal levels, leading to a reduction in tissue oxygen tension, and consequently to anaerobic cell metabolism, acidosis, and free radical generation.[1] According to one report, even at 12 mmHg, developed for laparoscopic cholecystectomy, and despite a patient's apparently normal hemodynamics,[15] intestinal ischemia and hepatic microcirculatory reduction developed.

As a consequence of intestinal ischemia, bacterial translocation during elevated IAP has been documented in two experimental studies, in both of which intra-abdominal hypertension lasted for only 60 min, but at levels of 15 mmHg and 25 mmHg, respectively.[16,17] Although it has been hypothesized that intestinally derived bacterial may serve to trigger a septic state, several investigators have expressed doubt about the clinical significance of bacterial translocation. Therefore, whether bacterial translocation due to raised IAP contributes to later septic complications and multiple organ dysfunction remains speculative and needs to be further investigated. Regardless of the relative importance of bacterial translocation as a causative factor in later septic complications, this study indicates that the deleterious effects of the combination of PEEP and IAP occur as early as within a 60-min period, this being a relatively short period of time. Thus, it could be hypothesized that in a similar clinical situation, when the time interval could be considerably longer, the splanchnic tissue damage occurring may be nonreversible.

The results of this study demonstrate that under these experimental conditions, PEEP ventilation and IAP act cumulatively on the abdominal viscera, leading to a dramatic deterioration in splanchnic blood flow. Although data need to be reproduced clinically, PEEP-ventilated patients treated in surgical intensive care units, being candidates for the development of intra-abdominal hypertension, must be monitored for abdominal pressure elevation by means of simple bladder manometry, as well as for splanchnic ischemia by gastric tonometry.

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