

# Prospective study on the effect of abdominal hypertension on intestinal mucosal barrier injury during laparoscopic surgery

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## Research article

**Keywords:** Abdominal pressure, Intestinal mucosal barrier, Damage, Laparoscopic surgery

**Posted Date:** April 17th, 2020

**DOI:** <https://doi.org/10.21203/rs.2.11014/v2>

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# Abstract

**Background** Prolonged and high intraperitoneal pressure may lead to impaired intestinal mucosal blood perfusion, increase the risk of surgery and complications, and affect the postoperative recovery of patients. However, the literature reports on the effect of abdominal hypertension on gastrointestinal function mainly focus on animal experiments, and there are few clinical reports. Our study intends to explore the effect of increased CO<sub>2</sub> pneumoperitoneum pressure during laparoscopy on intestinal mucosal barrier injury.

**Methods** A prospective study was conducted on 180 patients who underwent laparoscopic cholecystectomy in the First People's Hospital of Shuangliu District, Chengdu from October 2017 to March 2018. A randomized, single-blind, controlled study was performed in the 180 patients who were allocated into the 10 mmHg group (1 mmHg=0.133 kPa), 12 mmHg group and 15 mmHg group based on a random number table and setting value of intraoperative CO<sub>2</sub> pneumoperitoneum pressure (10 mmHg, 12 mmHg and 15 mmHg). Main observation indexes such as intraoperative conditions and postoperative recovery were recorded, and the results of serum tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1), D-lactic acid, blood endotoxin levels, plasma diamine oxidase (DAO) activity were detected. The measurement data of normal distribution were expressed as mean ± standard deviation ( $\bar{x} \pm S$ ), and one-way analysis of variance was used for comparison between groups. The measurement data with non-normal distribution are represented by M (QR) and non-parametric test is adopted, count data were presented as the n(%), and comparison among groups was analyzed using the chi-square test.

**Results** 180 patients were screened out, 60 patients in each group. Eight patients dropped out during the study (2 in 10 mmHg group, 1 in 12 mmHg group and 5 in 15 mmHg group). All patients in the three groups were cured and discharged without bleeding, secondary bile duct stones, bile leakage and reoperation. There was no significant difference in serum TNF-α, IL-1, D-lactic acid, endotoxin level and plasma diamine oxidase (DAO) among the three groups after operation ( $P > 0.05$ ).

**Conclusion** Laparoscopic surgery under 15 mmHg CO<sub>2</sub> pneumoperitoneum did not cause intestinal mucosal barrier damage, and the operation under the pneumoperitoneum was safe and reliable.

**Registry** This study was registered with the Chinese Clinical Trial Registry with the registry number of ChiCTR1900023936. Registered 19 June 2019, retrospectively registered.

## Background

Intestinal mucosa is not only an important place for human body to digest and absorb nutrients, but also the largest storage organ of bacteria and the main portal for pathogenic microorganisms and toxins to enter the body. Intestinal mucosal barrier is composed of intestinal mucosal mechanical barrier, chemical barrier, biological barrier and immune barrier<sup>[1,2]</sup>, which can effectively prevent the excessive growth of bacteria in the small intestine and the occurrence of endotoxemia. However, under the influence of ischemia and hypoxia, hypoperfusion, severe trauma, surgery, stress, abdominal hypertension, nutritional disorders, bacterial endotoxin and long-term application of broad-spectrum antibiotics, all of these factors can lead to

intestinal barrier function damage, bacterial imbalance, excessive growth of intestinal bacteria and endotoxin, induce and aggravate systemic inflammatory response and multiple organ dysfunction [MODS], and eventually form a vicious cycle<sup>[3,4]</sup>. With the advent of the era of minimally invasive surgery, laparoscopic technology has been widely used in various clinical fields. Laparoscopic surgery requires CO<sub>2</sub> gas injection in the abdominal cavity to establish pneumoperitoneum to expand the surgical field, which directly leads to the increase of intra-abdominal pressure. Prolonged and high intraperitoneal pressure may lead to impaired intestinal mucosal blood perfusion, increase the risk of surgery and complications, and affect patients' postoperative recovery. However, the literatures about the effect of abdominal hypertension on gastrointestinal function mainly focus on animal experimental study<sup>[5-7]</sup>, but rarely on clinical report<sup>[8]</sup>, our study prospectively analyzed the patients who underwent laparoscopic cholecystectomy in our hospital from October 2017 to March 2018, during which different CO<sub>2</sub> pneumoperitoneum pressure was used for surgery, to explore the influence of different abdominal pressure on intestinal mucosal barrier, and the report is as follows:

## Methods

### 1.1 General information

A prospective study was performed in 180 patients with gallstones admitted to our hospital from October 2017 to March 2018. The patients were 20-81 years old, with an average of (62.5+7.7) years, including 64 males and 116 females. Inclusion criteria :(1) age range from 20 to 81 years; (2) the American society of anesthesiologists (ASA) grade I ~ II; (3) the imaging examination (color ultrasound, CT or MRI) was clearly cholelithiasis; (4) the patient agreed to undergo laparoscopic cholecystectomy. Exclusion criteria :(1) contraindication of laparoscopic surgery (such as extensive intraperitoneal adhesion, etc.); (2) emergency surgery; (3) preoperatively complicated with obvious intestinal obstruction or intestinal paralysis; (4) preoperative systemic inflammatory response syndrome and other diseases; (5) conversion to open surgery; (6) persistent uncorrected water electrolyte disturbance (e.g., hypokalemia, hypomagnesemia, etc ). Our study was a clinical randomized controlled trial, which was approved by the medical ethics committee of our hospital. Patients and their families were informed of the test method and operation method before operation, and informed consent was obtained and signed. The research project was registered in the Chinese clinical research registry with the registration number ChiCTR1900023936, which met the requirements of the Helsinki declaration in 1964.

### 1.2 methods

#### 1.2.1 grouping and processing methods

In this study, the standard formula  $N=2[\mu_{\alpha}+\mu_{\beta}/\delta/\sigma]^2+1/4\mu_{\alpha}^2$  was used to calculate the required sample size. Among them,  $\alpha=0.05$ ,  $\alpha$  takes both sides,  $\mu_{\alpha/2}=1.96$ ;  $\beta=0.1$ ,  $\mu_{\beta}=1.282$ .  $\delta$  is the difference between the mean values of the two populations, and  $\sigma$  is the population standard deviation. Based on the actual work analysis, the sample size estimation is assumed to be  $\delta/\sigma=0.6$ , and the theoretical sample size  $N$  is calculated as 60. In this study, a total of 180 subjects were studied in three groups.

A randomized single-blind controlled study was performed in the 180 patients who were allocated into the 10 mmHg group (1 mmHg=0.133 kPa) 12 mmHg group and 15 mmHg group based on a random number table and setting value of intraoperative CO<sub>2</sub> pneumoperitoneum pressure (10 mmHg 12 mmHg and 15 mmHg). Clinical data including age, sex, combined disease, ASA anesthesia stage and body mass index were collected. Laparoscopic cholecystectomy was performed by the same group of experienced surgeons, and the anesthesia was endotracheal intubation under general anesthesia.

### 1.2.2 Operation method:

1) **Instruments:** disposable trocar puncture device (Guangzhou dike company, batch number : 117121531), laparoscopic absorbable clip (Hangzhou shengshi technology co., LTD, batch number: 1711230101), laparoscopic instrument (manufacturer: zhejiang wanhe), high-frequency electrotome ICC-200 (erbo company, model: ICC-200).

2) **Operation methods:** preoperative preparation as routine fasting for 6 hours before surgery, water deprivation for 4 hours, routine skin preparation at the operation area, general anesthesia with endotracheal intubation. Procedure as patients were placed in supine position with head high and foot low and left semi-horizontal position (inclined 30°). The abdominal skin was routinely disinfected with iodine volts, and sterile towels were laid. After skin incision at the lower edge of umbilicus, a disposable puncture instrument was used to puncture to establish CO<sub>2</sub> pneumoperitoneum. The abdominal cavity was routinely probed during the operation, and the relationship between gallbladder morphology and adjacent tissues was observed, the gallbladder triangle structure was dissected clearly, and the gallbladder duct and gallbladder artery were separated. After clipping the gallbladder duct and gallbladder artery with absorbable clip, and which were cut off, the gallbladder was removed, the gallbladder bed electric coagulation hemostasis. According to the situation of hemorrhage and gallbladder inflammation to decide whether to place drainage tube, finally close the trocar hole.

3) **Postoperative treatment:** on the day after the operation, patients were given fasting water, oxygen, electrocardiogram monitoring, observation of vital signs, abdominal abnormal signs and drainage, and appropriate fluid supplementation to maintain the balance of water and electrolytes. On the first day after the operation, a liquid or semi-liquid diet was taken, review of color doppler ultrasound found no abnormality in the abdominal cavity, after second or third days postoperation, the drainage was pulled out.

### 1.3 observation indexes:

1) Intraoperative conditions of patients were recorded as operation mode, operation time, duration of CO<sub>2</sub> pneumoperitoneum, intraoperative blood loss, etc. 2) Venous blood was taken 24 hours after the operation to check the serum tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), blood d-lactic acid, endotoxin levels and plasma diamine oxidase (DAO) activity. 3) Postoperative complications as postoperative fever, bleeding, bile duct secondary stones, bile leakage and reoperation.

### 1.4 Statistical methods

SPSS19.0 software was used for statistical analysis of all the data. Measurement data were expressed as mean  $\pm$  standard deviation  $\bar{x} \pm s$ , and one-way analysis of variance was used for comparison between groups. The measurement data with non-normal distribution are represented by M (QR) and non-parametric test is adopted. The counting data were represented by n (%), and comparison among groups was analyzed using the chi-square test,  $P < 0.05$  was considered statistically significant.

## Results

### 2.1 Analysis of general data of three groups of patients

Gender, age, combined diseases (hypertension, diabetes, etc.), ASA classification of anesthesia, and body mass index of the three groups were not statistically significant ( $P > 0.05$ ), and the data were comparable (table 1). In our study, 8 patients withdrew from the study (2 patients in the 10mmHg group had severe inflammation, pneumoperitoneum depression, which could not expose the visual field, and the operation after raising the pneumoperitoneum pressure was excluded from the study. In the 12mmHg group, 1 patient transferred to laparotomy and was excluded from this study. In the 15mmHg group, 3 patients were removed due to high pneumoperitoneum pressure and anesthesia failure to tolerate the reduced pneumoperitoneum pressure to 12mmHg; 1 patient was transferred to laparotomy due to intraoperative peritoneal adhesion and difficulty in visual field exposure; another patient was found to have intraoperative complicated bile duct abnormality, and was removed into the group after changing the operation mode); the remaining 172 patients completed the operation according to the plan. There was no statistically significant difference among the three groups ( $P > 0.05$ ).

**Table 1 Analysis of general data of three groups of patients (case)**

Group	Number	Gender [M/F]	Age [ $\bar{x} \pm s$ , year]	BMI Kg/m <sup>2</sup>	Combined diseases [n%]	ASA [I/II]	Intraoperative bleeding (M [QR],ml)	CO <sub>2</sub> time (M [QR],min)	Operating time (M [QR],min)
0mmHg	60	19/41	48.8 $\pm$ 14.1	22.41 $\pm$ 3.45	5[8.3%]	10/50	10(10[10])	40(31[53])	44(34[58])
2mmHg	60	25/35	48.8 $\pm$ 12.3	22.75 $\pm$ 3.04	7[11.2%]	7/53	10(10[17.5])	44(30[58.75])	45(33[60])
5mmHg	60	20/40	46.9 $\pm$ 14.3	23.10 $\pm$ 3.09	8[13.3%]	8/52	10(10[10])	41(31[60])	45(34[62])
Test value		t=1.758	t=0.428	F= 0.699	$\chi^2=8.22$	$\chi^2=5.67$	$\chi^2=0.947^a$	$\chi^2=0.488^a$	$\chi^2=0.546^a$
P values		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05

Annotation: a is for non-parametric test, BMI is for body mass index.

### 2.2 Postoperative indicators of the three groups

All patients in the three groups had no postoperative wound bleeding, no bile duct secondary calculi, bile leakage or reoperation, and no significant fever. All patients were cured and discharged, and the difference was not statistically significant. There were no significant differences in serum TNF- $\alpha$ , IL-1, D-lactic acid, endotoxin level and plasma diamine oxidase (DAO) activity among the three groups ( $P > 0.05$ ) (Table 2).

Table 2 Comparative analysis of postoperative indicators in three groups

Group	Number	IL-1 (M [QR], ng/L)	DAO (M [QR], U/L)	TNF- $\alpha$ (M [QR], ng/L)	D-lactic acid (M [QR], mg/L)	Endotoxin (M [QR], EU/ml)
0mmHg	58	5.81 (4.50 6.30)	1.71 (0.72 2.45)	3.96 (1.28 9.10)	17.55 (12.09 30.57)	3.56 (3.10 5.79)
2mmHg	59	5.99 (4.66 7.11)	1.74 (0.94 3.15)	5.03 (2.41 10.14)	16.49 (10.78 34.42)	3.56 (3.08 5.79)
5mmHg	55	6.0 (4.60 6.44)	1.19 (0.60 2.18)	3.55 (2.58 10.46)	13.54 (9.78 29.95)	5.66 (3.10 5.82)
Test value		$\chi^2=1.077$	$\chi^2=4.362$	$\chi^2=1.165$	$\chi^2=1.347$	$\chi^2=1.564$
P values		>0.05	>0.05	>0.05	>0.05	>0.05

## Discussion

### 3.1 The relationship between abdominal hypertension and intestinal mucosal barrier

According to the expert consensus and treatment guidelines issued by the World Federation of Abdominal Septal Syndromes<sup>[9]</sup>, intra-abdominal pressure (IAP) refers to the steady intra-abdominal pressure; abdominal hypertension (IAH) could be diagnosed when persistent or repeated pathological elevation of IAP  $\geq 12$  mmHg. However, the establishment of pneumoperitoneum of CO<sub>2</sub> in laparoscopic surgery increases the intra-abdominal pressure to 12~15mmHg (1 mmHg= 0.133kPa), which is equivalent to the level I of intra-abdominal pressure. Persistent IAP >20mmHg (with or without abdominal perfusion pressure <60mmHg) and new organ dysfunction or failure can be diagnosed as abdominal compartment syndrome (ACS). The abdominal cavity is a closed space. When the pressure inside the abdominal cavity rises, it will compress the large arteries and viscera inside the abdominal cavity, affecting the blood supply of important viscera. Because the gastrointestinal tract is the most sensitive organ when the reaction is increased for IAP. When IAP > 20mmHg, intestinal mucosa and submucosa layer of significantly impaired blood perfusion<sup>[10]</sup>, intestinal ischemia can reduce oxygen supply and compensatory to improve the ability of intestinal uptake and utilization of oxygen, intestinal oxygen consumption increased significantly, produced a large number of acidic metabolites, organization pH decline, intestinal mucosa epithelial cells damaged edema, connection between the cell membrane and cell rupture, cell necrosis, epithelial shedding, then pathogenic bacteria, toxins and other harmful substances through the intestinal wall to the intestinal caused a series of adverse consequences. Under normal circumstances, the intestinal mucosal barrier plays an important role in maintaining the stability of the internal environment of the body. The intestinal mucosa can prevent the migration of intestinal bacteria and endotoxins to the outside of the intestine, and protect the body from the damage of food antigens, microorganisms and their harmful metabolites<sup>[11]</sup>. However, under the influence of ischemia and hypoxia, hypoperfusion, surgery, severe trauma, stress, abdominal hypertension, nutritional disorder, bacterial endotoxin and other factors, it can lead to impaired intestinal barrier function, dysbacteriosis, intestinal bacterial overgrowth, intestinal bacteria and endotoxin translocation, which can induce and aggravate systemic inflammatory response and multiple organ dysfunction (MODS), eventually form a vicious circle.

Due to the fact that intestinal mucosal barrier function injury is a common pathophysiological process of various severe stress reactions, the current understanding is not comprehensive, the diagnostic means are lacking, the diagnostic criteria are uncertain<sup>[12]</sup>, and the detection method directly reflecting the intestinal mucosal barrier function is still lacking. In clinical practice, most indirect methods are adopted for detection. The main detection methods<sup>[13-14]</sup> include: 1) determination of intestinal mucosal permeability, such as: sugar molecular probe (L/M), isotope, polyethylene glycol, D-lactic acid, plasma diamine oxidase (DAO) activity; 2) plasma endotoxin<sup>[21]</sup>; 3) gastrointestinal mucosal PH value; 4) determination of intestinal fatty acid binding protein (I-FABP). Different detection indexes were adopted to elaborate the relationship between intra-abdominal pressure and intestinal mucosal barrier from various aspects in our study, which can provide a more reliable theoretical basis: D-lactic acid is a metabolite of bacterial fermentation, which can be produced by various bacteria in the intestinal tract. When intestinal mucosa permeability increases, large amounts of D-lactic acid produced by intestinal bacteria enter the blood through the damaged mucosa. D-lactic acid dehydrogenase is absent in mammals. Therefore, D-lactic acid level in blood increases when intestinal mucosa is damaged and permeability increases, so detection of D-lactic acid level in blood can timely reflect the damage degree and permeability change of intestinal mucosa. Plasma diamine oxidase (DAO) is a highly active intracellular enzyme in the cytoplasm of villi cells in the upper mucosa of the intestinal mucosa of humans and all mammals. Its activity is closely related to nucleic acid and protein synthesis of intestinal mucosa cells. It is mainly distributed in the upper mucosa or villi of the intestinal mucosa, and other organs are much lower than small intestine. When intestinal mucosal cells die, the enzyme releases human blood, or enters the intestinal tract with intestinal mucosal cells, leading to increased DAO activity in the blood and intestinal tract. Studies have found that<sup>[15]</sup>, DAO is a landmark enzyme of intestinal injury, which can indirectly reflect the integrity and damage degree of intestinal mucosa.

The results of our study showed that different intraperitoneal pressures did not significantly change the activity of endotoxin, blood D-lactic acid and plasma diamine oxidase, with no statistically significant. The possible reason was that the establishment time of laparoscopic pneumoperitoneum in this study lasted only 0.5-2 hours, and the intestinal mucosal barrier injury could not be caused. Although Kozlik<sup>[16]</sup> found that the increase of pneumoperitoneal pressure during laparoscopic surgery for more than 30 minutes would lead to the occurrence of gastrointestinal peroxidation stress, the possible gastrointestinal injury was confirmed from the perspective of cytology. However, in our study showed that the transient intraperitoneal hypertension was not enough to change the intestinal mucosal barrier based on the analysis of laboratory indicators.

### **3.2 The relationship between intra-abdominal pressure and inflammatory mediators**

Under the condition of abdominal hypertension, the local immune environment of abdominal cavity will be changed, inflammatory factors play an important role in the acute phase reaction and their receptors regulate cytokine activity, which reflect the severity of inflammatory. The release of a large number of inflammatory factors in patients will cause damage to intestinal mucosal epithelial cells and damage to the tight junctions between cells, and also cause bacterial migration, release of endotoxin and aggravate

inflammatory reaction. Inflammatory factors closely related to the intestinal mucosal barrier include TNF- $\alpha$ , IL-1 [17-20], etc. The results of our study showed that different intraperitoneal pressure did not significantly change the level of inflammatory mediators, but this result was limited by the detection time, because existing research results showed that there was a time-effect relationship between elevated intraperitoneal pressure and serum levels of inflammatory mediators [8]. Therefore, monitoring the level of inflammatory mediators at different time points will help better reflect the true immune status of patients after surgery.

### 3.3 Credibility and limitations of the study

The negative results obtained in our study from the perspective of intestinal mucosal barrier injury confirmed that it was safe and reasonable to set CO<sub>2</sub> pneumoperitoneum pressure at or below 15mmHg in laparoscopic cholecystectomy, and provided a theoretical basis for setting pneumoperitoneum pressure in other laparoscopic surgeries. Its credibility was mainly reflected in the following aspects: 1) of the 180 patients enrolled patients, 8 patients (4.4%) withdrew from the study due to non-compliance with the inclusion criteria, which was consistent with the expected 10% follow-up loss rate. 2) the blind method was maintained throughout the whole process to eliminate possible bias as far as possible in our study. 3) common confounders such as pneumoperitoneum duration and operation time were eliminated by random grouping.

However, there are still some limitations in our study: 1) the operation time and CO<sub>2</sub> pneumoperitoneum establishment time are short, and the intra-abdominal pressure cannot be continuously monitored after surgery, which limits the reliability of the results. 2) This study only analyzes the indirect indicators related to intestinal mucosal barrier injury, lack of pathological examination. Since the detection time was 24 hours after surgery, slight intestinal mucosal barrier injury could be repaired by itself, so increasing the frequency of laboratory detection indicators would make the results more reliable.

## Conclusions

In conclusion, the increased intra-abdominal pressure caused by the transient CO<sub>2</sub> pneumoperitoneum during the operation will not cause the intestinal mucosal barrier injury of patients after laparoscopic surgery, and has no impact on the systemic immune function and stress response of the body. It is safe and reliable to perform laparoscopic surgery when the CO<sub>2</sub> pneumoperitoneum pressure is set at or below 15mmHg.

## Abbreviations

TNF- $\alpha$  =tumor necrosis factor alpha IL-1= interleukin 1

DAO= diamine oxidase                      MODS= multiple organ dysfunction

ASA= anesthesiologists                      IAP =intra-abdominal pressure

ACS= abdominal compartment syndrome

# Declarations

## **Ethics approval and consent to participate:**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (This research project was approved by the medical ethics committee of The First People's Hospital of Shuangliu district, Chengdu city, China. Number :20160303).

All participants in the study received written informed consent and signed confirmation.

**Consent for publication:** Not applicable

**Availability of data and material:** All of our original data can be found in the Chinese Clinical Trial Registry (<http://www.chictr.org.cn/index.aspx>). Registry number of ChiCTR1900023936.

**Competing interests:** Author Yong Yang declares that he has no conflict of interest. Author Xin Kang declares that he has no conflict of interest. Author Xingjian Yang declares that he has no conflict of interest. Author Yi Hu declares that he has no conflict of interest. Author Rong Chen declares that she has no conflict of interest. Author Lin Xu declares that she has no conflict of interest. Author Yu Zhou declares that she has no conflict of interest. Author Liangsong Zhao declares that he has no conflict of interest. Author Yong Zhang declares that he has no conflict of interest.

**Funding:** This study was funded by health and family planning commission of Sichuan province, China (grant number :16 PJ223). The role of the funding: Funding from the fund.

**Authors' contributions** HY, ZLS and ZY collected and managed all the data in this study. CR and ZY conducted the examination of test specimens, XL conducted data analysis and statistics, KX and YXJ participated in the operation, and YY was the main manager of the study and the main contributor to the manuscript. All the authors read and approved the final manuscript.

**Acknowledgements** Not applicable

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