Int J Clin Exp Med 2017;10(11):15424-15431
www.ijcem.com /ISSN:1940-5901/IJCEM0056796

Original Article

A temporary peri-operative reduction in exhaled nitric oxide under different ventilation strategies in laparoscopic cholecystectomy

Dongchun Wang, Dan Wang, Hui Wang, Xin Pi, Da An, Ligang Li, Lei Guo, Mingjuan Li, Desheng Liu, Enyou Li

Department of Anesthesiology, The First Affiliated Hospital of Harbin Medical University, Harbin, People's Republic of China

Received March 5, 2017; Accepted September 27, 2017; Epub November 15, 2017; Published November 30, 2017

Abstract: Laparoscopic surgery leads to increased intra-abdominal pressure, cranial displacement of the diaphragm, decreased pulmonary compliance, and reduced functional residual capacity. The resulting pneumoperitoneum may lead to atelectasis and lung injury. Exhaled nitric oxide (eNO) is recognized as a biomarker of pulmonary and non-pulmonary diseases. We therefore investigated the perioperative change in eNO levels in laparoscopic cholecystectomy under different ventilation strategies. Patients scheduled for laparoscopic cholecystectomy under general anesthesia were submitted to ventilation with 0 (group Z) or 5 cm H_2O (group P) positive end-expiratory pressure. eNO, forced vital capacity (FVC), and forced expiratory volume in one second (FEV1) were measured at the bedside preoperatively, postoperatively, and during the following two days. eNO levels decreased significantly in patients recovering from general anesthesia, but the levels were restored one or two days after surgery in both groups. FVC and FEV1 were significantly decreased postoperatively and during the following two days in both groups. eNO was neither significantly correlated with FVC nor FEV1. In conclusions, a temporary perioperative reduction in eNO levels was observed in two different ventilation strategies in laparoscopic cholecystectomy, which may be due to small airway injury and increased carbon dioxide pressure in the blood as a result of pneumoperitoneum.

Keywords: Exhaled nitric oxide, laparoscopic cholecystectomy, mechanical ventilation

Introduction

Laparoscopic surgery has been accepted as the best option for treatment of gallbladder diseases owing to rapid recovery to normal activity, diminished postoperative pain, and reduced hospital stay [1]. It is accomplished by insufflating carbon dioxide, a highly soluble and nonflammable gas, into the peritoneal cavity. The intra-abdominal pressure is increased by intraperitoneal gas insufflation, which leads to cranial displacement of the diaphragm, decreased pulmonary compliance and lung volume, reduced functional residual capacity (FRC), increased resistance, and ventilation-perfusion mismatch [2]. Pneumoperitoneum may lead to decreased arterial oxygenation because of increased atelectasis [3]. Pneumoperitoneum may also induce lung injury through inflammation and the oxidative stress pathway [4]. In addition, atelectasis resulting from pneumoperitoneum and re-expansion might aggravate lung injury in laparoscopic surgery [5].

Volume-controlled and pressure-controlled ventilation are both effective modes for laparoscopic surgery. However, there is no consensus about the best perioperative ventilation mode [6, 7]. Positive end-expiratory pressure (PEEP) may be beneficial for patients during laparoscopic surgery through attenuating the drop in arterial oxygen resulting from pneumoperitoneum. It may also prevent alveolar atelectasis and cyclical recruitment by improving lung compliance and ventilation-perfusion balance [8].

Exhaled nitric oxide (eNO) is currently recognized as a biomarker of pulmonary and non-pulmonary diseases [9], and its role in acute lung injury has been reported [10]. Our group found that preoperative eNO might be used to assess the risk of postoperative pulmonary complications (PPCs). Patients with eNO values less than 30.2 ppb were found to be at a lower risk of PPCs [11], although eNO levels decreased postoperatively after laparotomy owing to ventilation-related lung injury [12]. In this study,

Table 1. Demographic and operative properties

Characteristics	Group Z (N=50)	Group P (N=50)	*P* value
Age (years)	53.82±12.61	51.74±10.00	0.36*
Male sex (n; %)	30 (60%)	30 (60%)	1.00Δ
Body height (cm)	165 (158.75-170)	165 (160-171.25)	0.27†
Body weight (kg)	65.20±9.87	67.22±10.88	0.33*
BMI (kg/m^2)	24.24±2.47	24.41±3.04	0.76*
Smoking (n; %)	6 (12%)	13 (26%)	0.07Δ
Hypertension (n; %)	10 (20%)	13 (26%)	0.48Δ
Peri-operative			
Pneumoperitoneum time (s)	48.50 (32-70.50)	37 (29-63)	0.1†
Sufentanil (μg)	20 (20-25.75)	25 (20-30)	0.2†
Infusion volume (ml)	1000 (500-1000)	1000 (500-1000)	0.71†

Data presented as median (25-75%) and mean ± SD. BMI = Body mass index, Group Z: ventilated at 0 cm H_2O PEEP, Group P: ventilated at 5 cm H_2O PEEP, *: independent-samples t-test, Δ: Pearson's Chi-square test, †: Kruskal-Wallis test.

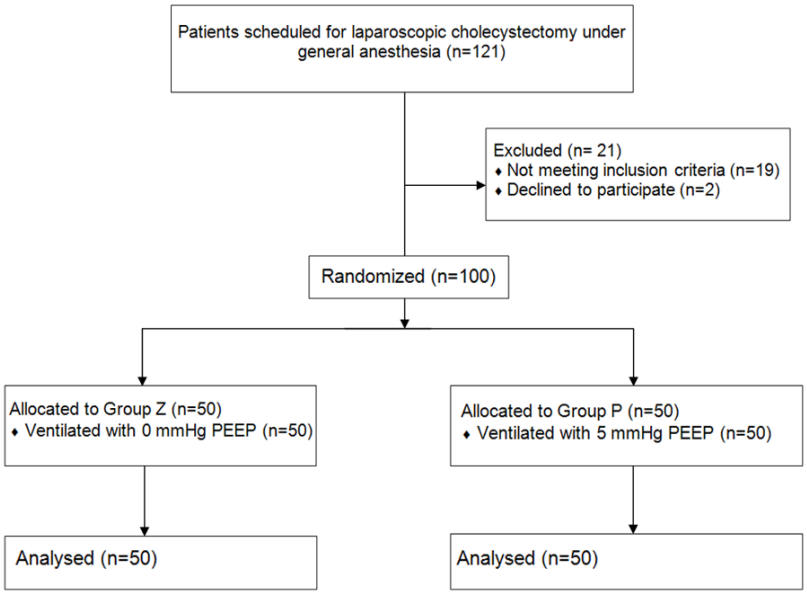

Figure 1. Flow Diagram. 121 patients were observed during the study period; 21 patients were excluded due to decline to participate or not meeting inclusion criteria. Finally 100 patients were included for analysis.

Table 2. Peri-operative exhaled nitric oxide values

	Pre-operation	Post-operation	Day 1	Day 2	*P* value
Group Z	14.08±6.94	11.64±7.04*	14.58±5.79	15.60±6.40	(g) 0.17 (t)<0.001
Group P	13.64±6.84	9.90±5.39*	14.28±6.06	13.44±5.55	(g*t) 0.34

*: *P*<0.05 compared with pre-operation. Overall time effect *p* (t), group effect *p* (g), interaction between overall effects *p* (g*t), Group Z: ventilated at 0 cm H_2O PEEP, Group P: ventilated at 5 cm H_2O PEEP, Day 1: one day after surgery, Day 2: two day after surgery. Peri-operative exhaled nitric oxide values were analyzed by repeated measurement ANOVA.

we investigated the changes in eNO during laparoscopic surgery under different ventilation strategies.

Materials and methods

The present study was approved by the Ethics Committee of Harbin Medical University (No. 201-314), and written informed consent was obtained from patients prior to study enrollment. We have been registered at the China clinical trials registry. The register number is ChiCTR-ROC-17011853. Inclusion criteria: 1. Patients scheduled for laparoscopic cholecystectomy under general anesthesia. 2. Patients were fasted for at least 8 hours. 3. Patients were abstained from foods containing nitrates (lettuce, spinach, cabbage, sausages) for at least 12 hours. 4. Patients were restrained from smoking for at least 72 hours. Exclusion criteria were as follows: body mass index greater than 35 kg cm^{-2}, history of asthma and chronic obstructive pulmonary disease, respiratory symptoms or infections in the last four weeks, and corticosteroid therapy in the last year (**Table 1**). Ultimately, 100 patients were included for analysis (**Figure 1**).

Data measurement

Patients were randomly divided into two groups; group Z, ventilated at 0 cm H_2O PEEP, and group P, ventilated at 5 cm H_2O

Table 3. Intra-operative procedures

	T_1	T_2	T_3	T_4	*P* value
Sys-pressure (mm Hg)					(g) 0.87
Group Z	124.66±23.71	118.58±24.95	127.36±20.18	118.85±19.83	(t) 0.007
Group P	118.86±24.24	117±27.82	129.34±17.62	129.63±18.84	(g*t) 0.01
Dia-pressure (mm Hg)					(g) 0.49
Group Z	75.42±15.70	75.38±16.42	80±12.54	74.30±12.08	(t)<0.001
Group P	69.90±16.23	73.04±16.02	80.74±11.32	80±15.08	(g*t) 0.003
Heart rate (bpm)					(g) 0.96
Group Z	76.28±14.34	65.04±11.21	68.96±13.96	69.33±13.68	(t)<0.001
Group P	68.16±12.65	63.42±11.36	69.68±11.55	72.89±11.67	(g*t) 0.003
VT (ml)					(g) 0.31
Group Z	410.18±58.40	426.66±72.40	430.92±67.41	424.48±85.83	(t) 0.01
Group P	382.58±83.79	400.94±84.93	407.08±82.41	415.11±97.39	(g*t) 0.71
Breath rate (bpm)					(g)<0.001
Group Z	12.24±0.87	12.28±0.67	12.94±1.62	13.20±1.95	(t) 0.02
Group P	12.12±0.48	12.04±0.28	12.10±0.51	12.06±0.34	(g*t) 0.01
Ppeak (mm Hg)					(g) 0.001
Group Z	12.46±2.60	17.60±3.61	18±3.77	17.58±3.16	(t)<0.001
Group P	14.78±2.99	19.68±3.64	19.30±3.23	19.37±3.08	(g*t) 0.52
Pplat (mm Hg)					(g) 0.001
Group Z	10.44±2.52	15.84±3.64	16.18±3.35	16.10±2.87	(t)<0.001
Group P	12.82±2.69	18.16±3.62	17.20±3.21	17.71±2.87	(g*t) 0.23
$P_{ET}CO_2$ (mm Hg)					(g)<0.001
Group Z	34.20±4.02	31.28±4.05	35.86±4.20	34.93±3.10	(t)<0.001
Group P	36.10±3.82	34.02±4.18	39.56±4.50	40.49±5.13	(g*t) 0.004
Compl (l/cmH_2O)					(g) 0.37
Group Z	51.50±13.54	31.26±9.22	30.78±10.69	32.43±10.62	(t)<0.001
Group P	51.12±16.89	33.48±11.18	35.06±13.88	37.37±15.95	(g*t) 0.11
MAC (%)					(g) 0.08
Group Z	0.44±0.20	0.97±0.20	0.93±0.18	0.88±0.24	(t)<0.001
Group P	0.30±0.19	0.90±0.45	0.80±0.39	0.77±0.37	(g*t) 0.27

Overall time effect *p* (t), group effect *p* (g), interaction between overall effects *p* (g*t). Sys-pressure: systolic pressure; Dia-pressure: diastolic pressure; Ppeak: peak airway pressure; Pplat: plateau inspiratory pressure; $P_{ET}CO_2$: end-tidal carbon dioxide partial pressure; Compl: compliance. MAC: minimal alveolar concentration. T_1: after intubation and pre-pneumoperitoneum; T_2: just after completion of insufflation; T_3: 15 min post-pneumoperitoneum; and T_4: 30 min post-pneumoperitoneum. Group Z: ventilated at 0 cm H_2O PEEP. Group P: ventilated at 5 cm H_2O PEEP. Intra-operative data were analyzed by repeated measurement ANOVA.

PEEP. Lungs were ventilated using volume-controlled ventilation (Drager Fabius GS premium; Drager Medical AG, Lubeck, Germany), with a tidal volume of 6 to 8 mL kg^{-1} of ideal body weight [calculated as the height (in cm) minus 100 in men and minus 105 in women], respiratory rate of 12 breaths min^{-1}, and inspiratory to expiratory ratio of 1:2. The respiratory rate was increased when end tidal carbon dioxide partial pressure ($P_{ET}CO_2$) >45 mm Hg. Except for SpO_2 monitoring, electrocardiography, $P_{ET}CO_2$, non-invasive arterial pressure (measured every 5 min), heart rate, bispectral index (BIS) (Datex Ohmeda S/5 Avance; GE Healthcare, Helsinki, Finland), peak airway pressure (Ppeak), plateau inspiratory pressures (Pplat), compliance (Compl), and tidal volume (VT) were monitored using a D-lite transmitter connected to the monitor. Hemodynamic and respiratory parameters were recorded at four time points: T_1, after intubation and pre-pneumoperitoneum; T_2, just after completion of insufflation; T_3, 15 min post-pneumoperitoneum; and T_4, 30 min post-pneumoperitoneum (**Table 3**).

Table 4. Variables of blood gas parameters during laparoscopic surgery

	Group Z			Group P		
	Pre-pnp	Post-pnp	*p* value	Pre-pnp	Post-pnp	*p* value
HB	146.46±16.08	135.81±17.98	<0.001	150.02±15.29	139.84±14.88	<0.001
HCT	39.54±4.36	36.70±4.95	<0.001	39.86±7.01	37.09±6.69	<0.001
PH	7.43±0.05	7.35±0.05	<0.001	7.44±0.04	7.34±0.05	<0.001
BE	0.43±3.15	-1.03±2.78	0.001	0.88±2.16	-0.86±2.39	<0.001
$PaCO_2$	36.96±4.24	44.31±6.36	<0.001	36.92±4.17	45.52±5.41	<0.001
PaO_2	108.06±65.66	229.25±104.33	<0.001	76.22±37.42	163.94±67.02	<0.001
LAC	0.99±0.42	1.25±1.05	0.09	1.10±0.98	0.87±0.50	0.10

Pre-pnp: pre-pneumoperitoneum; Post-pnp: post-pneumoperitoneum; HB: hemoglobin; HCT: hematocrit; PH: potential of hydrogen; BE: base excess; $PaCO_2$: partial pressure of carbon dioxide; PaO_2: partial oxygen pressure; LAC: lactate; Group Z: group 0 mm Hg PEEP; Group P: group 5 mm Hg PEEP. Variables of blood gas parameters during laparoscopic surgery were analyzed by paired t-test.

A NO analyzer (NIOX; Aerocrine, Solna, Sweden) was used to measure eNO levels in patients scheduled for laparoscopic cholecystectomy following guidelines of the American Thoracic Society and the European Respiratory Society. The patients were seated comfortably with a nose clip, exhaled as much air as they could, and then inhaled NO-free air for 2 to 3 s through the mouth to total lung capacity. After closing the velopharyngeal aperture to eliminate interference of NO from the nose, the patients were informed to exhale at a constant rate of 50 mL s^{-1} through a filter for 10 s. The procedure was repeated after the patient recovered from general anesthesia at the post anesthesia care unit for the following two days (**Table 2**).

Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) were measured at the bedside using a portable spirometer (MasterScreen GE; Care Fusion, San Diego, CA) immediately after eNO levels were obtained. Arterial blood was collected before induction of anesthesia and at the end of the pneumoperitoneum by using heparinized syringes and was analyzed by GEM Premier 3000 PAK (Instrumentation Laboratory Company, MA, USA) (**Table 4**).

Anesthesia protocols

Patients were induced using 0.3 to 0.5 μg kg^{-1} sufentanil, 1 to 2 mg kg^{-1} propofol, 0.2 mg kg^{-1} cisatracurium, and 1 mg kg^{-1} lidocaine (1%) and endotracheal intubation. Anesthesia was maintained by inhalation of sevoflurane [end tidal concentration ≥0.6 minimal alveolar concentration (MAC)] to preserve BIS index in the range of 40 to 60. Cisatracurium (0.05 mg kg^{-1}) was applied every 40 min.

Statistical analysis

The data are presented as mean ± SD or median and interquartile range (25 to 75%) as appropriate. The normality of the distribution was tested with the Kolmogorov-Smirnov test. For demographic and operative properties analysis, normally distributed numerical variables were assessed using the independent-samples t-test, categorical variables were assessed using the Pearson's Chi-square test, non-normal distribution variables were compared using the Kruskal-Wallis test. A repeated-measures ANOVA analysis was conducted for peri-operative exhaled nitric oxide values and intra-operative procedures analysis. A paired t-test was used for variables of blood gas parameters analysis. A $P<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 13.0.

Results

Patients' characteristics and the relationship with eNO

Patients' characteristics are presented (**Table 1**). There were no between-group differences in characteristics and operative properties.

Perioperative changes of eNO, FVC and FEV1

A main time effect was observed in eNO levels ($P<0.001$), but no significant differences between groups ($P=0.17$) or in group and time interactions ($P=0.34$) were found (**Table 2**).

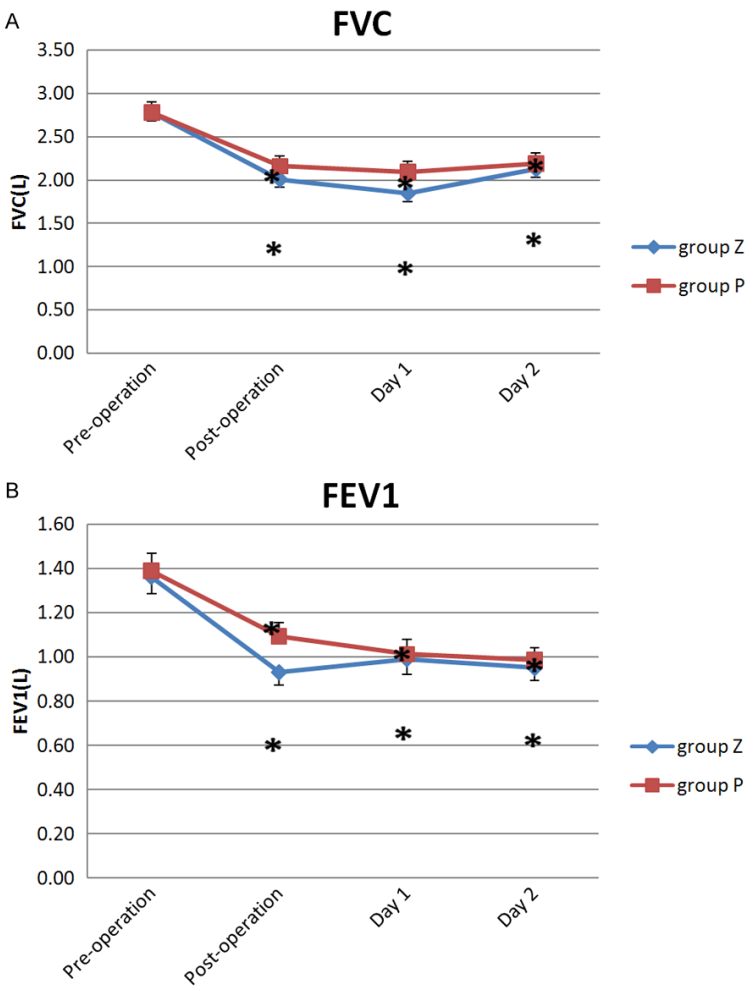

Figure 2. A. Peri-operative FVC; B. Peri-operative FEV1. FVC: forced vital capacity, FEV1: forced expiratory volume in one second, Day 1: one day after surgery, Day 2: two day after surgery. *: $P<0.05$ compared with pre-operation.

eNO levels were reduced significantly after the patients recovered from general anesthesia, but the levels were restored one or two days after surgery in both groups (**Table 2**). FVC and FEV1 were significantly decreased post-operatively and during the following two days in both groups ($P<0.05$) (**Figure 2A** and **2B**). Pearson correlation analysis showed that eNO was not correlated with FVC or FEV1 ($P>0.05$).

Intra-operative parameters and blood gas

Intra-operative parameters were significantly changed within 30 min of insufflation. No significant differences were observed between the two groups in blood pressure, heart rate, tidal volume, and MAC. In contrast, Ppeak, Pplat, and $P_{ET}CO_2$ were significantly different between the two groups. Compliance after insufflation was higher in patients of group P than of group Z, but no significant difference was observed between the two groups (**Table 3**). Most blood gas parameters were significantly changed during laparoscopic surgery by the application of pneumoperitoneum. In contrast, no significant changes were observed in lactate (LAC) between both groups (**Table 4**).

Discussion

Pneumoperitoneum-induced injury is known to occur in intra-abdominal as well as extra-abdominal organs such as the lung. Oxidative stress and lipid peroxidation lead to biological membrane impairment and subsequent cell damage and tissue injury, which are responsible for lung injury after pneumoperitoneum [13]. In addition, increased inflammatory cytokine levels after pneumoperitoneum cause damage to cell structures, capillary endothelium, and pulmonary tissue, which also result in lung injury [14]. In our study, eNO levels were significantly reduced in patients awakened from general anesthesia compared with preoperative levels, although they were restored at the first or second day postoperation in both groups.

eNO is generated by various cell types and is produced through conversion of L-arginine to L-citrulline by nitric oxide synthase (NOS). Three isoforms of NOS are described: neuronal NOS (NOS I or nNOS), inducible NOS (NOS II or iNOS), and endothelial NOS (NOS III or eNOS) [15]. eNOS and nNOS produce small amounts of NO depending on calcium levels, and are believed to regulate blood flow and play a role as neurotransmission, respectively. Although eNOS and nNOS are expressed constitutively, iNOS is induced only in some cell types by inflammatory cytokines.

Large amounts of NO are produced during inflammation, which may exert pro-inflammatory effects [16, 17]. It was described that oxidative stress and ischemia reperfusion injury due to laparoscopic surgery increased, whereas plasmatic levels of NO after carbon dioxide pneumoperitoneum decreased, which might be primarily ascribed to decreased activity of eNOS and increased activity of iNOS [18]. Use of an arginase inhibitor reduces pneumoperitoneum-induced oxidative stress and inflammation and decreases lung injury [19]. These changes in NOS activity may partially explain our findings. It is also possible that small airway injuries result from the abnormal shear stress [20] and depletion of surfactant [21] caused by repeated opening and closing of small airways by mechanical ventilation. Because eNO is primarily generated by cells in small airways, it can be used to predict small airway injury [22].

Our results show that eNO levels were restored within two days of post-operation, which suggests that the inhibitory effects due to pneumoperitoneum and small airway injury are temporary and reversible. To our knowledge, it is the first time that changes in perioperative eNO levels in laparoscopic surgery were observed. Moreover, the larger sample size and longer observation time confer greater reliability and robustness to our results. Further studies are needed to elucidate the exact mechanism underlying this phenomenon.

PEEP (5 cm H_2O) improves arterial oxygenation during prolonged laparoscopic surgery [23], however high level of PEEP might lead to hemodynamic change or barotrauma [24]. In our study, eNO was not increased by the application of PEEP. In contrast, Persson et al. pointed out that application of PEEP increased the concentration of eNO in a dose-dependent manner, which might be attributed in part to vagal mechanisms [25]. The increase in eNO induced by PEEP is significantly attenuated after bilateral vagotomy. In addition, eNO is not affected by either L-type calcium channel inhibition or by the local anesthetic and ganglion blocker xylocaine. In contrast, gadolinium chloride completely suppresses PEEP-induced nitric oxide formation, which is not associated with pulmonary edema or PEEP-induced changes in stretch of the airways [26]. The mechanism of eNO induction by PEEP is still unclear. It is possible that mechanical stretching of lung tissue induces eNO in response to PEEP, which in turn changes the FRC. Pulmonary capillaries are compressed by PEEP and blood flow is reduced, resulting in less scavenging of NO by hemoglobin [27]. The lack of eNO induction by PEEP in the present work may be explained by the duration or intensity of PEEP in laparoscopic surgery being insufficient to prevent pneumoperitoneum-related lung injury.

FVC and FEV1 decreased significantly within two days post-operation, although neither correlated with changes in eNO levels. Similar results have also been observed in asthma patients. Mappa et al. suggested that eNO levels are not related to FEV1 or FVC [28]. In contrast, the predicted FEV1 correlated with eNO levels in lung cancer patients. Patients with predicted FEV1<80% show higher levels of eNO than those with predicted FEV1≥80% [29]. The causes underlying these inconsistent results are likely diverse, although we suspect that it is due to different disease pathogeneses. More research is needed to clarify this issue.

Ppeak, Pplat, and $P_{ET}CO_2$ values showed significant differences between the two groups, and compliance after insufflation was higher in patients of group P than of group Z, although no significant difference was observed. The results suggest that 5 cm H_2O PEEP may improve lung compliance to some extent, which is consistent with previously published work [30]. The lack of statistically significant differences in lung compliance between the two groups in our study led us to speculate that the duration and intensity of pneumoperitoneum during laparoscopic cholecystectomy may be insufficient to cause markedly reduced lung compliance and function.

In conclusion, a temporary perioperative reduction in eNO levels was observed in two different ventilation strategies in laparoscopic cholecystectomy, which may be due to small airway injury and increased carbon dioxide pressure in the blood as a result of pneumoperitoneum.

Acknowledgements

This work was partly supported by the Wu Jieping Medical Foundation (No. 320.6700.1-157) and the Key Technologies R&D Program of Heilongjiang Province (No. GC12C305-5), to which we convey our sincere gratitude. We also thank all the volunteers in the study.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Enyou Li, Department of Anesthesiology, The First Affiliated Hospital of Harbin Medical University, Harbin, People's Republic of China. Tel: 13845109928; E-mail: enyouli@sina.com

References

[1] Himal HS. Minimally invasive (laparoscopic) surgery. Surg Endosc 2002; 16: 1647-52.
[2] Safran DB and Orlando R 3rd. Physiologic effects of pneumoperitoneum. Am J Surg 1994; 167: 281-6.
[3] Duggan M and Kavanagh BP. Pulmonary atelectasis: a pathogenic perioperative entity. Anesthesiology 2005; 102: 838-54.
[4] Gao S, Guan S, Li H, Su A and Wang Y. Ameliorating effects of low tidal volume ventilation with associated hypercapnia on pneumoperitoneum-induced lung injury by inhibition of toll-like receptor. J Clin Exp Med 2015; 8: 1814-23.
[5] Grabowski JE and Talamini MA. Physiological effects of pneumoperitoneum. J Gastrointest Surg 2009; 13: 1009-16.
[6] Aydın V, Kabukcu HK, Sahin N, Mesci A, Arici AG, Kahveci G and Ozmete O. Comparison of pressure and volume-controlled ventilation in laparoscopic cholecystectomy operations. J Clin Respir 2016; 10: 342-9.
[7] Sen O, Umutoglu T, Aydın N, Toptas M, Tutuncu AC and Bakan M. Effects of pressure-controlled and volume-controlled ventilation on respiratory mechanics and systemic stress response during laparoscopic cholecystectomy. Springerplus 2016; 5: 298.
[8] Meininger D, Byhahn C, Mierdl S, Westphal K and Zwissler B. Positive end-expiratory pressure improves arterial oxygenation during prolonged pneumoperitoneum. Acta Anaesthesiol Scand 2005; 49: 778-83.
[9] Bucca C, Cicolin A, Guida G, Heffler E, Brussino L and Rolla G. Exhaled nitric oxide (FENO) in non-pulmonary diseases. J Breath Res 2012; 6: 027104.
[10] Boshier PR, Hanna GB and Marczin N. Exhaled nitric oxide as biomarker of acute lung injury: an unfulfilled promise? J Breath Res 2013; 7: 017118.
[11] Pi X, Wang C, Li Y, Zheng J, Cui Y, Guo L, Lin Z, Zhang X and Li E. Preoperative FeNO as a screening indicator of pulmonary complications after abdominal surgery in patients over 60 years old. J Breath Res 2015; 9: 036004.
[12] Cui Y, Pi X, Wang C, Liu S, Gong Y, Wang Y, Zhang F, Shi J, Lin Z, Zhang X and Li E. Effects of different ventilation strategies on exhaled nitric oxide in geriatric abdominal surgery. J Breath Res 2015; 9: 016006.
[13] Pross M, Schulz HU, Flechsig A, Manger T, Halangk W, Augustin W, Lippert H and Reinheckel T. Oxidative stress in lung tissue induced by CO(2) pneumoperitoneum in the rat. Surg Endosc 2000; 14: 1180-4.
[14] Ozmen MM, Zulfikaroglu B, Col C, Cinel I, Isman FK, Cinel L and Besler TH. Effect of increased abdominal pressure on cytokines (IL1 beta, IL6, TNFalpha), C-reactive protein (CRP), free radicals (NO, MDA), and histology. Surg Laparosc Endosc Percutan Tech 2009; 19: 142-7.
[15] Ricciardolo FL, Sterk PJ, Gaston B and Folkerts G. Nitric oxide in health and disease of the respiratory system. Physiol Rev 2004; 84: 731-65.
[16] Persson MG, Gustafsson LE, Wiklund NP, Moncada S and Hedqvist P. Endogenous nitric oxide as a probable modulator of pulmonary circulation and hypoxic pressor response in vivo. Acta Physiol Scand 1990; 140: 449-57.
[17] Fischer A and Hoffmann B. Nitric oxide synthase in neurons and nerve fibers of lower airways and in vagal sensory ganglia of man. Correlation with neuropeptides. Am J Respir Crit Care Med 1996; 154: 209-16.
[18] Shin S, Na S, Kim OS, Choi YS, Kim SH and Oh YJ. Effect of pneumoperitoneum on oxidative stress and inflammation via the arginase pathway in rats. Yonsei Med J 2016; 57: 238-46.
[19] Cho JS, Oh YJ, Kim OS and Na S. The effects of arginase inhibitor on lung oxidative stress and inflammation caused by pneumoperitoneum in rats. BMC Anesthesiol 2015; 15: 129.
[20] D'Angelo E, Pecchiari M, Baraggia P, Saetta M, Balestro E and Milic-Emili J. Low-volume ventilation causes peripheral airway injury and increased airway resistance in normal rabbits. J Appl Physiol (1985) 2002; 92: 949-56.
[21] D'Angelo E, Pecchiari M and Gentile G. Dependence of lung injury on surface tension during low-volume ventilation in normal open chest rabbits. J Appl Physiol (1985) 2007; 102: 174-82.
[22] D'Angelo E, Koulouris NG, Della Valle P, Gentile G and Pecchiari M. The fall in exhaled nitric oxide with ventilation at low lung volumes in rabbits: an index of small airway injury. Respir Physiol Neurobiol 2008; 160: 215-23.
[23] Meininger D, Byhahn C, Mierdl S, Westphal K and Zwissler B. Positive end-expiratory pressure improves arterial oxygenation during prolonged pneumoperitoneum. Acta Anaesthesiol Scand 2005; 49: 778-83.
[24] Lee HJ, Kim KS, Jeong JS, Shim JC and Cho ES. Optimal positive end-expiratory pressure dur-

ing robot-assisted laparoscopic radical prostatectomy. Korean J Anesthesiol 2013; 65: 244-250.
[25] Persson MG, Lonnqvist PA and Gustafsson LE. Positive end expiratory pressure ventilation elicits increases in endogenously formed nitric oxide as detected in exhaled air of rabbits. Anesthesiology 1995; 82: 969-74.
[26] Bannenberg GL and Gustafsson LE. Stretch-induced stimulation of lower airway nitric oxide formation in the guinea-pig: inhibition by gadolinium chloride. Pharmacol Toxicol 1997; 81: 13-8.
[27] Carlin RE, Ferrario L, Boyd JT, Camporesi EM, McGraw DJ and Hakim TS. Determinants of nitric oxide in exhaled gas in the isolated rabbit lung. Am J Respir Crit Care Med 1997; 155: 922-7.
[28] Mappa L, Cardinale F, Camodeca R, Tortorella ML, Pietrobelli A, Armenio L and Boner AL. Exaled nitric oxide and air trapping correlation in asthmatic children. Allergy 2005; 60: 1436-9.
[29] Liu PF, Zhao DH, Qi Y, Wang JG, Zhao M, Xiao K and Xie LX. The clinical value of exhaled nitric oxide in patients with lung cancer. Clin Respir J 2016; [Epub ahead of print].
[30] Cinnella G, Grasso S, Spadaro S, Rauseo M, Mirabella L, Salatto P, De Capraris A, Nappi L, Greco P and Dambrosio M. Effects of recruitment maneuver and positive end-expiratory pressure on respiratory mechanics and transpulmonary pressure during laparoscopic surgery. Anesthesiology 2013; 118: 114-22.