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Cardiovascular and respiratory effects of carbon dioxide pneumoperitoneum in the domestic rabbit *(Oryctolagus cuniculus)*

Claudia Kabakchiev, Alexander Valverde, Ameet Singh, Hugues Beaufrère

Abstract

The objective of this study was to evaluate the effect of intra-abdominal pressure (IAP) on cardiorespiratory parameters during pneumoperitoneum with carbon dioxide in domestic rabbits. Six juvenile female New Zealand white rabbits were assigned to randomized sequences of IAP (0, 4, 8 mmHg) in a crossover study. The following parameters were measured at each IAP: direct arterial blood pressure (ABP); cardiac output, (CO), cardiac index, and stroke volume index (CI, SVI); heart rate; end-tidal carbon dioxide ($ETCO_2$); arterial blood gases ($PaCO_2$, PaO_2); peak inspiratory pressure (PIP); and peripheral oxygen saturation (SpO_2). Between IAPs, the abdomen was desufflated for a 5-minute washout period. Mixed linear regression models were used for statistical analysis. Heart rate, SpO_2, and ABP were not significantly affected by IAP, although there was a positive increase in ABP with IAP. Partial pressure of carbon dioxide ($PaCO_2$) was increased at an IAP of 8 mmHg and $ETCO_2$ and PIP were greater with each IAP applied. Cardiac output and CI were significantly decreased with IAP and, although SVI showed the same trend, it was not statistically significant. In conclusion, pneumoperitoneum with carbon dioxide causes an increase in $ETCO_2$, $PaCO_2$, and PIP, whereas cardiac output and CI decrease. These cardiorespiratory changes should be considered when determining the optimal IAP for laparoscopic procedures in rabbits.

Résumé

L'effet de différentes pressions intra-abdominales (IAP) sur les paramètres cardiorespiratoires durant un pneumopéritoine à CO_2 a été évalué sur 6 femelles lapins néo-zélandais. Les lapins furent assignés à des séquences aléatoires d'IAP (0, 4, 8 mmHg) dans une étude croisée. Les paramètres suivants furent mesurés à chaque IAP : pression artérielle directe (ABP), débit cardiaque, indice de volume systolique et cardiaque (SVI, CI), fréquence cardiaque, CO_2 de fin d'expiration ($ETCO_2$), gaz sanguins artériels ($PaCO_2$, PaO_2), pic de pression inspiratoire (PIP) et saturation en oxygène (SpO_2). Entre chaque IAP, l'abdomen était dégonflé pendant une période de 5 minutes. Des modèles de régression linéaire mixte ont été utilisés pour l'analyse statistique. La fréquence cardiaque, le SpO_2, et l'ABP ne furent pas affectés significativement par l'IAP, bien qu'il y eût une augmentation de l'ABP avec l'IAP. La $PaCO_2$ était augmentée a une pression de 8 mmHg et le $ETCO_2$ et le PIP augmentaient avec chaque pression. Le débit cardiaque et le CI étaient significativement diminués avec une augmentation de l'IAP et, bien que le SVI montraient la même tendance, ces baisses n'étaient pas statistiquement significatives. En conclusion, un pneumopéritoine avec du CO_2 entraine une augmentation de la $ETCO_2$, du $PaCO_2$, et du PIP, alors que le débit cardiaque et la CI diminuent. Ces changements cardiorespiratoires doivent être pris en compte pendant la détermination de la pression intra-abdominale optimale à utiliser pour des chirurgies laparoscopiques chez le lapin.

(Traduit par les auteurs)

Introduction

As laparoscopy is frequently carried out in veterinary practice, it is important that the physiological effects of the resulting induced pneumoperitoneum are well-established (1). Rabbits are common pets and are also used as research and teaching models for pediatric endosurgery (2,3). A clear understanding of the cardiovascular and respiratory effects of pneumoperitoneum on this species will help to improve the safety and management of these animals under general anesthesia. Since visualization of abdominal organs and working space are improved as gas is insufflated into the abdomen, it would be appealing to maximize intra-abdominal pressure (IAP), but doing so can be detrimental to ventilation, cardiac function, and perfusion (4). With concurrent consideration of the change in working space with intra-abdominal pressure, it will be possible to make recommendations on the optimal IAP for use in rabbit laparoscopic procedures.

Although only a few studies have examined the cardiovascular effects of pneumoperitoneum in rabbits (5), it seems that the effects resemble those seen in humans, pigs, dogs, and cats (4,6–8). In general, the IAP produced by insufflation causes decreased venous return, due to compression of the vena cava, and simultaneous decreases in cardiac output. This is associated with increases in systemic vascular resistance. Arterial blood pressure does not change in a consistent manner, but is often increased (4,8–10). Heart rate also tends to be increased, which may be partially due to the cardiostimulatory effects of elevated arterial partial pressure of carbon dioxide ($PaCO_2$) during insufflation with carbon dioxide (9,11).

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Respiratory parameters are also known to be affected by pneumoperitoneum, largely due to reduced diaphragmatic excursion and pulmonary compliance as intra-abdominal pressure increases (4,11). Based on previous canine and porcine models, induction of pneumoperitoneum decreases tidal volume or increases peak inspiratory pressure (PIP), depending on whether ventilation is spontaneous or controlled (7,8). As a result, $PaCO_2$ and end-tidal carbon dioxide ($ETCO_2$) increase. This is due in part to ventilatory changes, but also due to diffusion of carbon dioxide from the abdomen into the bloodstream (11–13). The increase in $PaCO_2$ will ultimately lead to changes in blood pH and will negatively affect the arterial partial pressure of oxygen (PaO_2) (14,15).

Despite the use of rabbits as research models for laparoscopy in humans, there are few studies that examine the specific effects of varying pneumoperitoneal pressures on cardiovascular and respiratory parameters in this species (5,14,15). The anatomy of rabbits differs from that of pigs and dogs due to the relatively small thoracic volume and large gastrointestinal system. This may influence how pneumoperitoneum affects respiration and local perfusion. This study aims to compare cardiovascular and respiratory parameters at 0, 4, and 8 mmHg IAP in order to improve anesthetic recommendations for rabbits undergoing laparoscopy. These IAPs were selected due to their clinical relevance. Based on our previous research, sufficient laparoscopic working space should be attainable with an IAP of 8 mmHg (16), although further increases in pressure may be clinically unnecessary.

Based on our current understanding, it was hypothesized that cardiac output would be depressed with increasing IAP as previously described, but that the cardiostimulatory effects of increased $PaCO_2$ might help to maintain heart rate and blood pressure. We also hypothesized that $PaCO_2$, $ETCO_2$, and peak inspiratory pressure (PIP) would increase, as has been reported in rabbits and other species. This information will assist in developing guidelines for pneumoperitoneal pressure during laparoscopic procedures in rabbits.

Materials and methods

Animals

Six specific-pathogen-free, 4- to 5-month-old female New Zealand white rabbits (Charles River Laboratories, Saint-Constant, Quebec) were used. The rabbits weighed 3.02 to 3.53 kg. The same rabbits were involved in a study on laparoscopic working space before this research and were therefore allowed 7 d of recovery from the previous anesthetic event (16). Physical examinations were carried out at the start of the study before general anesthesia. The study protocol was reviewed and approved by the Animal Care Committee of the University of Guelph, in accordance with guidelines set by the Canadian Council on Animal Care.

Anesthesia and instrumentation

Food was withheld for 15 to 60 min and the rabbits were then premedicated with intramuscular (IM) midazolam (Sandoz Canada, Boucherville, Quebec), 1 mg/kg body weight (BW) and buprenorphine (Vetergesic; Sogeval UK, Sheriff Hutton, York, UK), 0.05 mg/kg BW. After at least 20 min, the right marginal auricular vein was catheterized with a 24-gauge intravenous catheter (BD Canada, Mississauga, Ontario). The rabbits were induced with intravenous (IV) propofol (Pharmascience, Montreal, Quebec), 8 to 10 mg/kg BW, intubated blindly in lateral recumbency using a 4-mm uncuffed endotracheal tube, and connected to the anesthetic machine (Datex Ohmeda; DRE Medical, Louisville, Kentucky, USA) using a circle circuit. The end-tidal isoflurane concentration was maintained at 2.0% to 2.2%. Isoflurane (IsoFlo; Zoetis Canada, Kirkland, Quebec) was provided with an oxygen (100%) flow rate of 2 L/min using intermittent positive pressure ventilation (IPPV) delivered by an electronically controlled, volume-cycled ventilator (S/5 Aespire 7900 Ventilator; GE Healthcare, Madison, Wisconsin, USA) at a rate of 12 breaths/min and a tidal volume of 15 to 17 mL/kg BW. An isotonic solution (Plasma-Lyte A; Baxter Healthcare, Deerfield, Illinois, USA) was administered intravenously during the anesthetic procedure at 10 mL/kg BW per hour. Cefazolin (Fresenius Kabi Canada, Toronto, Ontario), 20 to 25 mg/kg BW was administered intravenously before the first skin incision to prevent perioperative infection.

Rabbits were instrumented in the first 30 min of anesthesia for monitoring of electrocardiography, heart rate (HR), direct arterial blood pressure [(ABP) including systolic (SBP), diastolic (DPB), and mean (MBP)], peripheral pulse oximetry placed on the digits, esophageal temperature, $ETCO_2$ and end-tidal isoflurane concentrations, and specific spirometry variables (tidal volume, PIP) using a multiparameter monitor (S/5 Anesthesia Monitor, GE Healthcare).

A 24-gauge catheter (BD Canada) was placed in the central auricular artery for measuring direct arterial blood pressure and for blood sampling using heparinized syringes (AirLife; CareFusion, Yorba Linda, California, USA) to measure $PaCO_2$, PaO_2, sodium, and hemoglobin (ABL800 Flex Radiometer, Instrumentation Laboratory, London, Ontario). Cardiac output (CO) was measured using lithium dilution (LiDCO Plus; LiDCO, London, UK) by attaching a lithium chloride sensor (LiDCO Sensor) to the side port of a 3-way valve connected to the arterial catheter. Extension tubing was attached to the 3-way valve, connected to a blood collection bag, and blood passed through a peristaltic pump (LiDCO Flow Regulator) that produced a blood flow rate of 4 mL/min across the sensor. Lithium chloride (LiDCO, London, UK), 0.006 mmol/kg BW was injected into the marginal ear vein catheter and flushed with 2 mL of isotonic saline 8 s after starting the injection phase on the LiDCO computer. The arterial hemoglobin and sodium levels required by the LiDCO computer were determined immediately before CO was measured.

Cannula placement

The rabbits were placed in dorsal recumbency and the abdomen was clipped and aseptically prepared for surgery. A #15 scalpel blade was used to make a skin incision along the ventral midline approximately 1 cm caudal to the umbilicus and 4-0 polydioxanone stay sutures (PDS II; Ethicon, Johnson & Johnson Medical Products, Somerville, New Jersey, USA) were placed on either side of the *linea alba* to elevate the body wall and facilitate placement of the trocar/cannula assembly. Initially, a small incision was made with the scalpel and then a 3.5-mm graphite trocar/cannula assembly (Karl Storz Endoscopy America, El Segunda, California, USA) was inserted into the abdomen. A 2.7-mm 30° angle sheathed rigid endoscope (Karl

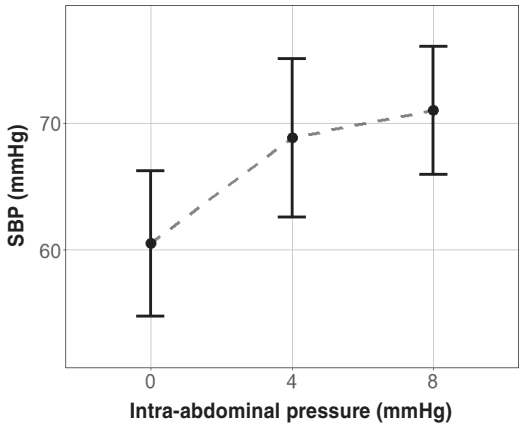

Figure 1. The effect of intra-abdominal pressure (IAP) (in mmHg) on systolic arterial blood pressure (SBP) (in mmHg), displayed in mean and standard error. A similar positive trend in blood pressure was seen for mean and diastolic pressures, although this effect was not statistically significant.

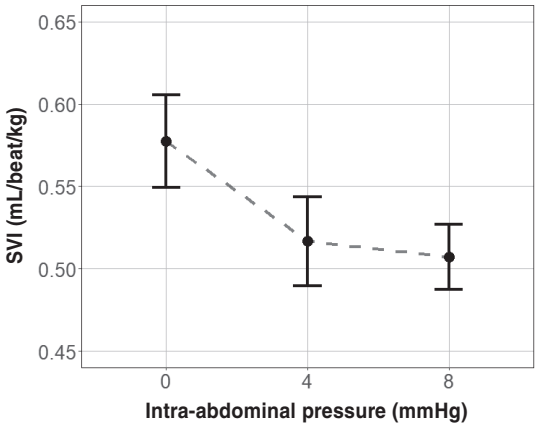

Figure 2. The effect of intra-abdominal pressure (IAP) (in mmHg) on the stroke volume index (SVI) (in mL/beat/kg), displayed in mean and standard error. The trend of decreasing SVI when IAP is applied mirrors the trend in cardiac output, although this effect was not statistically significant.

Storz Endoscopy America) was used to visualize abdominal organs and confirm proper placement of the cannula within the abdomen.

Experimental procedure

The design was a crossover study balanced for carry-over effects using two 3 × 3 Latin squares generated by an R statistical package (Version 3.4.1; R Core Team, R Foundation for Statistical Computing, Vienna, Austria) and each rabbit was randomly assigned to a random sequence of 3 IAPs (0, 4, 8 mmHg). The pressures used were selected based on a previous assessment that 4 and 8 mmHg provided appropriate laparoscopic working space (16). Mechanical insufflation (Highflow 40L Insufflator; Stryker, Kalamazoo, Michigan, USA) with carbon dioxide was maintained using a flow rate of 1 L/min at the desired IAP for at least 5 min before collecting an arterial blood sample to measure sodium, hemoglobin, $PaCO_2$, and PaO_2 (ABL800 Flex Radiometer). The remaining variables, including SBP, DBP, MBP, HR, CO, $ETCO_2$, PIP, and peripheral oxygen saturation (SpO_2), were measured at each IAP after 15 min of equilibration. A 5-minute period of zero pneumoperitoneum was applied before the next pressure in the random sequence was established. From these variables, cardiac index (CI) and stroke volume index (SVI) were calculated.

After applying all IAP treatments, the abdomen was purged of CO_2 with manual pressure and the cannula was removed. Abdominal incisions were closed using 4-0 polydioxanone suture (PDS II; Ethicon) in a simple interrupted pattern for the *linea alba* and 4-0 poliglecaprone 25 suture (Monocryl; Ethicon) in a continuous intradermal pattern for apposing the skin.

Post-anesthetic management

Meloxicam (1 mg/kg BW, IV) (Metacam 20 mg/mL Injectable; Boehringer Ingelheim, Burlington, Ontario) and flumazenil (Sandoz Canada), 0.025 mg/kg BW, half intravenously and half subcutaneously, were administered to each rabbit before extubation. All catheters were removed and the rabbits returned to their pens once they were responsive and sitting upright. For post-operative analgesia, they all received buprenorphine (Vetergesic; Sogeval, Manchester, UK), 0.05 mg/kg BW, subcutaneously 6 to 8 h after the initial premedication. Those rabbits that seemed to be in more pain post-operatively received additional meloxicam (Metacam 1.5 mg/mL Oral Suspension; Boehringer Ingelheim), 1 mg/kg BW, orally once daily or buprenorphine (Vetergesic; Sogeval UK), 0.05 mg/kg BW, subcutaneously at least 8 h apart as deemed appropriate. Vital parameters were assessed twice daily for 3 d after anesthesia.

Statistical analysis

The statistical software R (Version 3.4.1) was used to fit mixed linear regression models with each cardiovascular and respiratory parameter as an outcome variable. Due to the crossover nature of this study, rabbit ID was added to the model as a random effect; IAP and order of pressure in the sequence were fixed effects. Cardiovascular and respiratory parameters were assessed for correlation using Pearson correlation coefficients. They were applied as fixed effects in models only if they were not moderately to strongly correlated ($-0.65 < r < 0.65$) with the outcome measure and if they improved the fit of the model based on the Akaike information criterion (AIC). Assumptions of linearity, homoscedasticity of residuals, and normality of residuals were verified. Residual plots were used to look for outliers. Type-III analysis of variance was carried out on the fixed effects and Tukey adjustment was applied for *post-hoc* comparisons. Statistical significance was set at an alpha of 0.05. All figures were created using the "ggplot2" data visualization package of R (17).

Results

A heart murmur was noted in 1 rabbit. Although echocardiographic examination revealed significant tricuspid dysplasia, it was deemed that it would not interfere with the objectives of the study. This rabbit was assessed for any outlying results during data analysis, but all findings were similar to those of the other rabbits and the rabbit was not excluded from the study.

There was no statistically significant difference in heart rate (HR) based on the 3 treatments (IAP of 0, 4, and 8 mmHg; $P = 0.5956$) or based on the order in which pressures were applied ($P = 0.5730$).

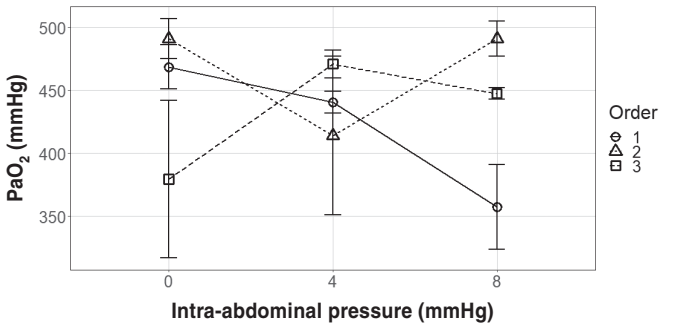

Figure 3. The effect of intra-abdominal pressure (IAP) (in mmHg) on arterial partial pressure of oxygen (PaO_2) (in mmHg), displayed in mean and standard error, accounting for the order in which the IAP was applied in the pressure sequence. There was a significant interaction effect between IAP and the order ($P = 0.0166$).

There was also no significant difference in SpO_2 across IAP ($P = 0.4096$) and order ($P = 0.4096$).

Although there was a positive trend towards increased ABP, the changes for SBP (Figure 1), MBP, and DBP were not significantly affected by IAP (SBP $P = 0.0611$; MBP $P = 0.0732$; DBP $P = 0.0816$) or order in the sequence of IAP (SBP $P = 0.3338$; MBP $P = 0.2406$; DBP $P = 0.2575$). There was a strong positive correlation between SBP and HR (Pearson correlation coefficient, $r = 0.7176$, $P = 0.0008$) and a moderate correlation between SBP and CO ($r = 0.6831$, $P = 0.0018$). There was also a moderate positive correlation between MBP and HR ($r = 0.6501$, $P = 0.0035$).

Stroke volume index (SVI) also decreased at an IAP of 4 and 8 mmHg compared to baseline. This effect was not significant ($P = 0.0613$), however, and neither was the effect of order in the sequence ($P = 0.7657$) (Figure 2).

For PaO_2, there was a significant interaction effect between IAP and the order in which pressures were applied in the sequence ($P = 0.0166$) (Figure 3). This effect could not be interpreted in any meaningful manner, but was included in the regression model. Intra-abdominal pressure (IAP) did not significantly affect the PaO_2 in this model ($P = 0.1710$).

There was a significant increase in $PaCO_2$ at 8 mmHg compared to 0 mmHg ($P = 0.0016$) and 4 mmHg ($P = 0.0076$) (Figure 4). Likewise, $ETCO_2$ was higher at each subsequent pressure (Figure 5); from IAP of 0 to 4 mmHg, the mean $ETCO_2$ increased from 43.8 to 47.3 mmHg ($P = 0.0424$) and from IAP of 4 to 8 mmHg, the mean increased from 47.3 to 52.3 mmHg ($P = 0.0071$). It was found that $ETCO_2$ and $PaCO_2$ were strongly correlated in their outcome measures ($r = 0.7747$, $P = 0.0002$).

End-tidal CO_2 and SpO_2 were included in the mixed regression models for CO and CI, since they improved the fit of the models and had only weak correlation with either outcome variable. In the final model, CO ($P = 0.0292$) and CI ($P = 0.0317$) were significantly decreased as intra-abdominal pressure was applied. Cardiac output (CO) decreased from a mean (± standard error) of 436.0 ± 44.0 mL/min without pneumoperitoneum to 385.3 ± 30.0 mL/min at 4 mmHg and 386.8 ± 28.0 mL/min at 8 mmHg (Figure 6). Cardiac output and CI demonstrated moderate positive correlations with heart rate ($r = 0.7324$ for CO, $P = 0.0005$; $r = 0.7222$ for CI, $P = 0.0007$).

Finally, PIP was significantly affected by intra-abdominal pressure ($P = 0.0001$) (Figure 7). Peak inspiratory pressure (PIP) increased from 15.3 mmHg to 17.2 mmHg when changing from an IAP of 0 to 4 mmHg ($P = 0.0489$). It subsequently increased from 17.2 mmHg to 20.7 mmHg as the IAP was increased to 8 mmHg ($P = 0.0015$).

Mild adverse effects were noted after anesthesia and abdominal insufflation in 3 rabbits. One rabbit developed dehiscence of the skin layer at the site of cannula placement. The incision was re-sutured and an "Elizabethan collar" was placed until the skin was completely healed. This rabbit received additional meloxicam, buprenorphine, and 10 mg/kg BW orally twice daily for 7 d of enrofloxacin (Baytril 50 mg/mL Injectable compounded to dilution of 20 mg/mL; Bayer Animal Health Canada, Mississauga, Ontario). Three rabbits had signs of abdominal discomfort on palpation in the first 24 h after the procedure. These rabbits received additional doses of meloxicam and buprenorphine and otherwise recovered uneventfully.

Discussion

Overall, the effect of carbon dioxide insufflation at pressures of 4 and 8 mmHg was as expected based on studies in humans and other animal models (4,6–8). A decrease in cardiac output (CO) and cardiac index (CI) was observed in this study and is believed to be due to decreased venous return and preload. The resultant effect is a decrease in stroke volume and this trend was demonstrated for SVI in this study. Stroke volume may also decrease with elevated systemic vascular resistance (SVR), although we did not measure SVR and its exact contribution cannot be determined. Nevertheless, there was a positive trend towards increased blood pressure, which may be related to an increase in SVR. In the present study, heart rate (HR) remained unchanged by IAP and, in the presence of a decreased SVI with higher IAP, CO or CI could not be maintained as high as for baseline (IAP of 0 mmHg).

In dogs, it is recommended that IAPs of less than 12 mmHg be used for laparoscopic procedures in order to prevent adverse effects on CO and other hemodynamic parameters (18). In cats, IAPs of 4, 8, and 15 mmHg did not cause changes in CI, HR, or SVI (19). Keeping IAP low may help minimize hemodynamic depression. The change in CO seen with carbon dioxide insufflation is well-tolerated in healthy patients, and in some circumstances, this may be a transient effect (20). However, patients with cardiovascular compromise or hypovolemia may be more severely affected. It should be noted that the rabbit with tricuspid dysplasia in this study did not appear to have more adverse effects than the other rabbits. Preconditioning, which is the application of pneumoperitoneal pressure for a short period of time before the longer pneumoperitoneum needed for a laparoscopic procedure, has also been shown in porcine models to attenuate some of the hemodynamic effects of high intra-abdominal pressures (21).

A previous study on the effect of IAP on hemodynamic parameters, including CO, in New Zealand white rabbits found an initial increase, followed by a decrease in CO as the pressure was gradually increased (22). In that study, IAP was applied by administering saline infusions into the abdomen. As a result, the concurrent cardiostimulatory effects of hypercapnia that occur with carbon dioxide insufflation were not accounted for (23). Hypercapnia is known to

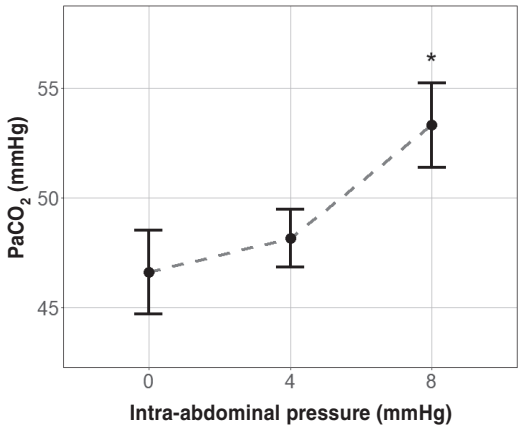

Figure 4. The effect of intra-abdominal pressure (IAP) (in mmHg) on the arterial partial pressure of carbon dioxide ($PaCO_2$) (in mmHg), displayed in mean and standard error. There was a significant increase in $PaCO_2$ at an IAP of 8 mmHg ($P \leq 0.0076$).

*** Significant difference from baseline.**

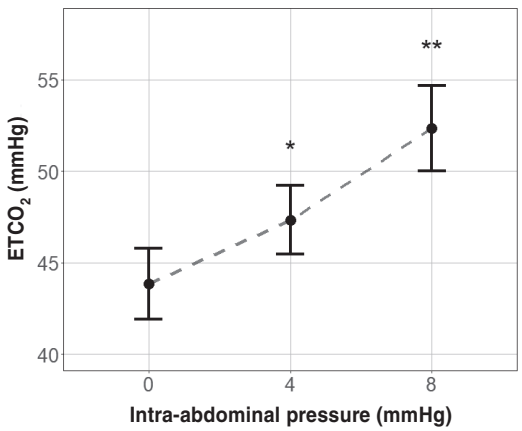

Figure 5. The effect of intra-abdominal pressure (IAP) (in mmHg) on the end-tidal carbon dioxide ($ETCO_2$) (in mmHg), displayed in mean and standard error. There was a significant increase in $ETCO_2$ at each subsequent IAP ($P \leq 0.0424$).

*** Significant difference from baseline.**
**** Significant difference from baseline and 4 mmHg.**

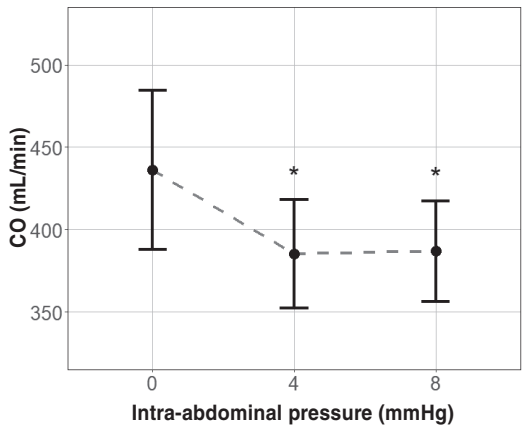

Figure 6. The effect of intra-abdominal pressure (in mmHg) on the cardiac output (CO) (in mL/min), displayed in mean and standard error. There was a significant decrease in cardiac output as IAP was applied ($P = 0.0292$).

*** Significant difference from baseline.**

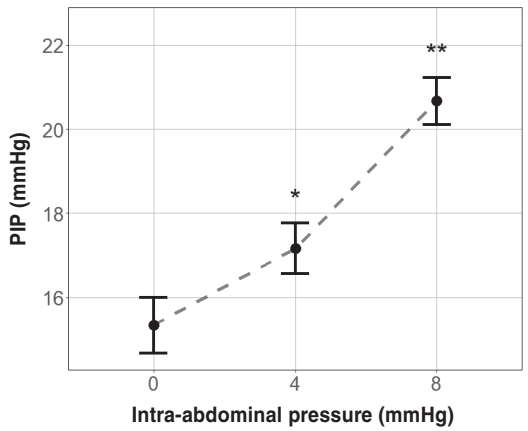

Figure 7. The effect of intra-abdominal pressure (IAP) (in mmHg) on the peak inspiratory pressure (PIP) (in mmHg), displayed as mean and standard error. There was a significant increase in PIP as IAP was applied ($P = 0.0001$).

*** Significant difference from baseline.**
**** Significant difference from baseline and 4 mmHg.**

activate the sympathetic nervous system, resulting in increases in ABP, HR, CO, and contractility (11,23). Using rabbits as models for pediatric laparoscopy, Sümpelmann et al also examined the effect of prolonged carbon dioxide pneumoperitoneum at 8 mmHg on CI and acid-base parameters and demonstrated a lower CI in the insufflated rabbits than in the control group (5), as corroborated by our current findings. In their study, however, there was an initial increase in CI during the first 30 min of insufflation at 8 mmHg due to an initial shift in blood volume from abdominal to thoracic vessels, with a decline in venous return seen only later (5).

The cardiostimulatory effect of hypercapnia was not significant enough in this study to result in a concurrent increase in heart rate (HR) and arterial blood pressure (ABP). Although increases in ABP have been reported with pneumoperitoneum, they are not always consistent (4,8,11). The change in ABP is related to release of catecholamines as a result of hypercapnia (9,19,23). In this study, a positive trend in blood pressure was seen as IAP increased, even though this effect was not statistically significant.

Maintaining a normal HR and ABP is not sufficient to ensure normal tissue perfusion. Previous studies, including in rabbits, have shown that changes in SVR and abdominal pressure with pneumoperitoneum affect perfusion of abdominal organs, particularly the splanchnic circulation (24–27). In addition, the effect of decreased blood pH may contribute to cellular damage of these abdominal tissues (28). Minimizing the IAP or time with pneumoperitoneum may help to mitigate these effects in individuals with impaired organ function. In addition to the effects caused by anesthesia and pneumoperitoneum alone, e.g., persistent carbon dioxide in the

abdomen and drying of peritoneal tissues, this change in splanchnic perfusion may contribute to post-anesthetic abdominal discomfort as seen in some of these rabbits.

As hypothesized, we also identified an increase in $PaCO_2$ and $ETCO_2$ consistent with previous studies in rabbits (14,15). These changes are expected to be the result of carbon dioxide diffusing into the bloodstream, as well as changes in pulmonary compliance and ventilatory pressure due to pneumoperitoneum (4,11). The effect of carbon dioxide alone is significant and has been examined in porcine models (12,13,29) and even a rabbit model (15) by comparing to insufflation with other gases. While the increase in $PaCO_2$ may initially improve cardiovascular function, however, it will ultimately lead to a decrease in blood pH and affect cellular metabolism. Increased ventilation is recommended to help eliminate carbon dioxide and prevent buildup.

The increase in peak inspiratory pressure (PIP) seen in these rabbits reflects how pneumoperitoneum affects ventilation. When using a volume-controlled ventilator, PIP is expected to increase due to pressure of pneumoperitoneal gas on the diaphragm and decreased lung compliance (4). As previously mentioned, the increased thoracic pressure with pneumoperitoneum leads to depression of venous return and decreases in CO.

The order in which IAPs were applied was important in determining the effect on PaO_2. There was an interaction between IAP and order in the sequence. Partial pressure of oxygen (PaO_2) may be influenced partially by time under anesthesia and other hemodynamic effects changing over time. While the change in PaO_2 seen here may have only minimal clinical significance, it highlights the importance of controlling for or factoring in sequence order in future crossover studies examining the effects of pneumoperitoneum on cardiovascular or respiratory parameters. It also emphasizes that crossover designs should be balanced for carry-over effects.

Several closely correlated variables were identified in this study, which is not unexpected given the close association between the cardiorespiratory parameters and the way they influence one another *in vivo*. For example, HR, ABP, and CO are all closely linked. Blood pressure is determined by CO and SVR, and CO in turn is determined by HR and SV. Therefore, these variables are expected to fluctuate together. Similarly, $ETCO_2$ and $PaCO_2$ are positively correlated since they reflect an increase in carbon dioxide in the blood and the body's attempt to eliminate the excess CO_2 (respiratory compensation).

The main limitation of the current study is the small sample size. Conducting this crossover study on rabbits of similar size, sex, age, and health status allowed for limited variability between individuals. No significant outliers were present in the group. One rabbit was identified as having a heart murmur and tricuspid dysplasia before being included in this study. This rabbit was not deemed to be an outlier and was not excluded from the sample population as the parameters measured in this rabbit were well within the ranges seen in the others.

Rabbits are frequently pets, are common laboratory animals, and are used as surgical models for pediatric patients (2,3). As a result, the use of laparoscopic procedures is becoming more common in this species. While the pneumoperitoneal pressure recommended for laparoscopy in rabbits will depend on the procedure being conducted, the previous evaluation of working space in rabbits would lead us to recommend an IAP of 4 to 8 mmHg since the percent increase in working space is less from 8 to 12 mmHg (16). Lower intra-abdominal pressures are particularly important for prolonged procedures or in patients with cardiovascular or respiratory diseases that would compromise their ability to respond to changes under anesthesia.

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