

# Pathogenesis of CO<sub>2</sub> Pneumoperitoneum-Induced Metabolic Hypoxemia in a Rabbit Model

Ospan A. Mynbaev, M.D., Ph.D., Carlos R. Molinas, M.D., Leila V. Adamyan, M.D., Ph.D.,  
Bernard Vanacker, M.D., Ph.D., and Philippe R. Koninckx, M.D., Ph.D.

---

## Abstract

**Study Objective.** To investigate the effects of carbon dioxide (CO<sub>2</sub>) pneumoperitoneum-induced changes in blood gases, acid-base balance, and oxygen homeostasis in rabbits.

**Design.** Prospective, randomized, controlled study (Canadian Task Force classification I).

**Setting.** University training and teaching center.

**Subjects.** Twenty-six adult female New Zealand white rabbits.

**Intervention.** Anesthesia and pneumoperitoneum.

**Measurements and Main Results.** In anesthetized rabbits arterial blood gases, acid-base balance, oxygenation values, and lactate concentrations were assayed during 2 hours. Spontaneous breathing, superficial and optimal ventilation without pneumoperitoneum, and with pneumoperitoneum at low (6 mm Hg) and higher (10 mm Hg) insufflation pressures were compared. The CO<sub>2</sub> pneumoperitoneum profoundly affected blood gases, acid-base balance, and oxygen homeostasis. Carboxemia with increasing end-tidal CO<sub>2</sub> and partial pressure of CO<sub>2</sub> ( $p < 0.001$ ), acidosis with decreasing pH ( $p < 0.001$ ), and base deficiency with decreasing actual base excess ( $p < 0.001$ ), standard base excess and standard bicarbonate and acid excess with increasing hydrogen bicarbonate ( $p < 0.05$  and  $< 0.01$ ) were found. Desaturation ( $p < 0.01$ ) with decreasing oxyhemoglobin  $p < 0.05$  and hemoglobin oxygen affinity ( $p < 0.01$ ) were also found. Carboxemia with acidosis was more pronounced with higher ( $p < 0.01$ ) than with lower ( $p > 0.05$ ) intraperitoneal pressures, and also with spontaneous breathing ( $p < 0.05$ ) and superficial ventilation ( $p < 0.001$ ) than with optimal ventilation, resulting in metabolic hypoxemia.

**Conclusion.** In superficially ventilated and spontaneously breathing rabbits, CO<sub>2</sub> pneumoperitoneum profoundly affected blood gases, acid-base balance, and oxygen homeostasis, resulting in metabolic hypoxemia. With optimal ventilation and low intraperitoneal pressure carboxemia, respiratory acidosis, and changes in oxygen metabolism were minimal.

(*J Am Assoc Gynecol Laparosc* 9(3):306–314, 2002)

---

From the Centre for Surgical Technologies, Faculty of Medicine, Katholieke Universiteit Leuven (Drs. Mynbaev, Molinas, and Koninckx); Departments of Obstetrics and Gynaecology (Dr. Koninckx) and Anaesthesiology (Dr. Vanacker), University Hospital Gasthuisberg, Leuven, Belgium; and Department of Operative Gynaecology, Scientific Centre for Obstetrics, Gynaecology and Perinatology; Russian Academy of Medical Sciences, Moscow, Russia (Drs. Mynbaev and Adamyan).

Supported by Karl Storz Endoscopy Belgium and Ethicon Endosurgery Belgium, and by The National Fonds voor Wetenschappelijk Onderzoek.

Address reprint requests to Ospan A. Mynbaev, M.D., Centre for Surgical Technologies, K.U. Leuven, Minderbroederstraat 17, B-3000 Leuven, Belgium; fax 3216337821.

Presented at the 10th congress of the European Society for Gynaecological Endoscopy, Lisbon, Portugal, November 22–24, 2001.

Accepted for publication January 22, 2002.

Pneumoperitoneum is essential to perform endoscopic surgical procedures in the abdominal cavity. Carbon dioxide (CO<sub>2</sub>) is generally used because of its high solubility in water and high exchange capacity in the lungs. Its concentration in expired gas can be easily monitored by capnography<sup>1-3</sup> and controlled by ventilation.<sup>2,4</sup>

The CO<sub>2</sub> pneumoperitoneum has local effects on peritoneum either directly or through desiccation or cooling. It is painful under local anesthesia. Disruption of morphologic integrity<sup>5</sup> can largely be prevented by humidification.<sup>6</sup> Changes in gastric and small bowel intramucosal pH<sup>7,8</sup> are probably direct effects of CO<sub>2</sub> pneumoperitoneum. Increased postoperative adhesions are known to be a direct effect.<sup>9-12</sup> It is unclear to what extent changes in microcirculation,<sup>8</sup> macrophage and immune function,<sup>13</sup> and tumor growth<sup>13,14</sup> can be prevented by humidification and warming.

Blood gases and acid-base balance change during CO<sub>2</sub> pneumoperitoneum,<sup>1-4</sup> with hypercarbia, acidemia, acidosis, and hypoxemia. Arterial and venous partial pressures of CO<sub>2</sub> (pCO<sub>2</sub>) increase,<sup>2,4,15</sup> and arterial and mixed venous pH,<sup>16,17</sup> O<sub>2</sub> saturation (sO<sub>2</sub>), and arterial pO<sub>2</sub> decrease. These changes affect cardiovascular and pulmonary function and are important in the perioperative and early postoperative periods, especially in patients with limited capacity to compensate.<sup>18</sup> During anesthesia, however, effects of CO<sub>2</sub> pneumoperitoneum on blood gases and acid-base parameters can be compensated for by infusions and by hyperventilation, during which inspiratory tidal volume is increased, depending on concentration of end-tidal CO<sub>2</sub>.

Effects induced by CO<sub>2</sub> pneumoperitoneum such as hypercarbia and hypoxia are associated with increasing sympathetic activity from a variety of subcortical centers.<sup>19</sup> Pneumoperitoneum also increases plasma concentrations of vasopressin, cortisol, and catecholamines such as noradrenaline, epinephrine, and norepinephrine.<sup>16,20-22</sup> The systemic effect of these substances is associated with changes in function in cardiovascular, respiratory, and urinary systems. A CO<sub>2</sub> pneumoperitoneum increases minute ventilation and peak inspiratory pressure,<sup>23</sup> pulmonary vascular resistance,<sup>20</sup> alveolar CO<sub>2</sub> concentration, calculated physiologic shunt,<sup>17</sup> central venous pressure, systolic and diastolic arterial pressures, and systemic vascular resistance,<sup>16,20</sup> and reduces liver and renal blood flow and urinary output.<sup>24</sup> During anesthesia in the

human, these effects are reduced by adequate hyperventilation and infusion therapy.

Since we demonstrated local effects of CO<sub>2</sub> pneumoperitoneum on adhesion formation and its prevention by adding small amounts of oxygen, we planned to evaluate the systemic effects of adding oxygen to CO<sub>2</sub>.<sup>25</sup> A prerequisite for this study was evaluation in the rabbit of the effect of ventilation parameters and pneumoperitoneum pressures on CO<sub>2</sub> pneumoperitoneum-induced changes in arterial blood gases, acid-base balance, and oxygen homeostasis.

## Materials and Methods

### Animals

Twenty-six adult female New Zealand white rabbits weighing between 2.7 and 3.0 kg were used. They were kept under standard laboratory conditions at a temperature between 20 and 25° C, and a relative humidity of 40% to 70%. They had a day cycle of 14 hours light and 10 hours dark, a standard laboratory diet (Hope Farms, Woerden, The Netherlands), and free access to food and water. The animals were housed at the Centre for Laboratory Animal Care of the Catholic University of Leuven, Belgium, and the experiment was approved by the institutional review animal care committee.

### Experimental Design

The experiment consisted of four groups: spontaneously breathing with 10 mm Hg (series I, 4 animals), superficial ventilation with 10 mm Hg (series II, 4), and optimal ventilation with 10 mm Hg (series IIIA, 4) or 6 mm Hg (series IIIB, 3) insufflation pressures for pneumoperitoneum; a control group for superficial ventilation (4) was established. These five groups were block randomized by day. Subsequently an additional control group for spontaneous breathing (3) and one for optimal ventilation (4) were established. Since no significant changes were observed in any control group, results of the three control groups were combined, leaving four experimental groups and one control group to be analyzed. Two animals died at the beginning of the experiment, one in series III and one in series I.

The animals were premedicated with an intramuscular injection of ketamine 1000, 30 mg/kg (Sanofi, Sante Animale; Benelux, Belgium) and 2% xylazine hydrochloridum solution 6 mg/kg (VMD,

Berendonk, Belgium). In spontaneously breathing rabbits anesthesia was maintained with inhalational halothane (2%, Fluothane; Zeneca, Destelbergen, Belgium) and oxygen mixed with room air (2 L/min) using a vaporizer (Dräger; Ballings, Belgium) and administered by mask. In mechanically ventilated rabbits after intubation with a 3.5-mm endotracheal tube (Sheridan Catheter Corp., New York, NY), inhalational anesthesia was performed with 2.5% halothane (Fluothane, Zeneca) mixed with oxygen and room air, using the vaporizer connected to a small animal ventilator (Harvard Apparatus Inc., Holliston, MA). The oxygen concentration in inspired gas (FiO<sub>2</sub>) was 70%. In the optimal ventilation series tidal volume was 11.3 ml/kg with a respiratory rate of 18 to 21 cycles/minute. In superficially ventilated animals tidal volume was 6.7 ml/kg with respiratory rate was 27 to 29 cycles/minute. Tidal volumes were chosen as described by others.<sup>26,27</sup> Respiratory rates were adjusted during pilot experiments to obtain baseline arterial pCO<sub>2</sub> lower than 45 mm Hg as described elsewhere.<sup>3,28</sup>

Pulse rate and sO<sub>2</sub> (in %) in peripheral blood (ear vessels, capillaries), end-tidal CO<sub>2</sub> (PETCO<sub>2</sub>), and respiratory pressure were monitored continuously with a pulse oximeter (Nellcor, Pleasanton, NE), a capnograph (Capnomac, Datex, Finland), and a manometer, respectively.

### Operative Procedure

Each animal was placed supine and the abdomen was shaved and disinfected with povidone iodine. Pneumoperitoneum was created with a 10-mm cannula (Apple Medical Corp., Marlboro, MA) placed caudal to the sternum. For pneumoperitoneum the Thermo-flotar Plus (Karl Storz, Tuttlingen, Germany) was used with a humidifier (Aquapor, Dräger Ballings) and a heating device (Opti Therm, Karl Storz) keeping the insufflation temperature between 35 and 37° C. A water valve was used to dampen changes in insufflation pressure. Taking into account the high exchange capacity of peritoneum and to maintain a 100% concentration of CO<sub>2</sub>, a continuous flow rate through the abdominal cavity of 80 ml/minute was used to remove constantly any O<sub>2</sub> that might have diffused from the circulation. To achieve this a 22-gauge catheter was inserted through the abdominal wall. This flow rate with heated and humidified CO<sub>2</sub> causes minimal desiccation.<sup>10</sup> Insufflation was done through the 10-mm cannula inserted superficially.

### Assays

In all animals the ear artery was catheterized with a 20-gauge catheter. Before blood samples were taken the syringe and catheters were rinsed with heparin in saline 5 IU/1000 ml. The first sample was taken before starting ventilation. After starting pneumoperitoneum, samples were taken every 30 minutes for 120 minutes. Syringes with blood samples were immediately put on ice and analyzed in duplicate in a blood gas analyzer (Radiometer, Copenhagen, Denmark). At the end of the experiment the animals were sacrificed with an intravenous injection of 0.3 ml/kg T61 (Hoechst Roussel Vet GmbH, Wiesbaden, Germany).

The following were measured: arterial blood gas values such as pH, pO<sub>2</sub>, and pCO<sub>2</sub>; blood oximetry values such as sO<sub>2</sub>, oxyhemoglobin (O<sub>2</sub>Hb), and reduced hemoglobin (RHb); oxygen status values such as total oxygen concentration (tO<sub>2</sub>) and oxygen tension at half saturation assessing the hemoglobin oxygen affinity (p50); and acid-base values such as concentrations of hydrogen carbonate (HCO<sub>3</sub>), standard bicarbonate (SBC), actual base excess (ABE), standard base excess (SBE), and concentration of total carbon dioxide (tCO<sub>2</sub>). Finally the lactate concentration was measured.

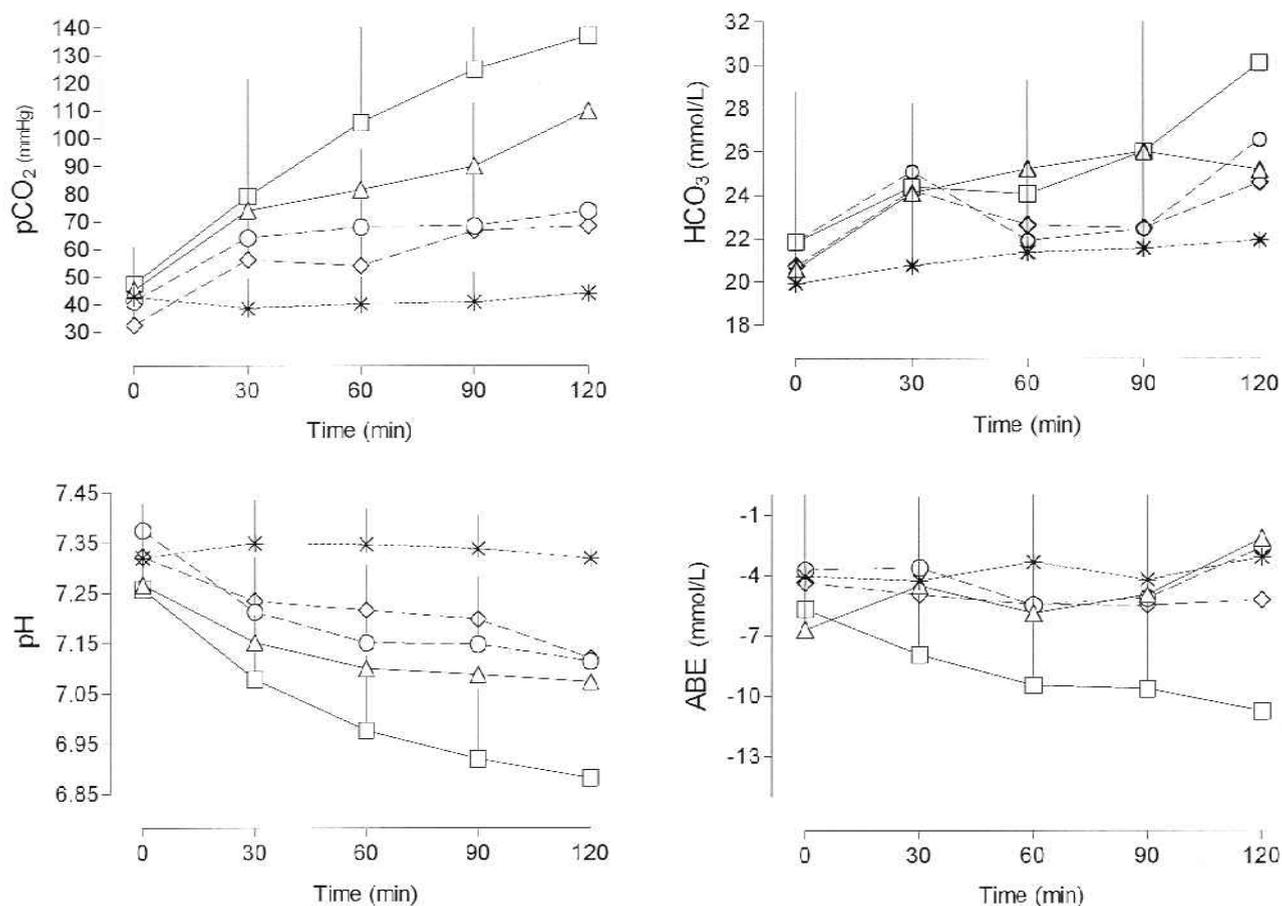
### Data Analysis

Mean ± SD are given unless stated otherwise. Data were analyzed using Graph Pad Prism (Graph Pad Software Inc., San Diego, CA). Differences between control and CO<sub>2</sub> pneumoperitoneum groups, as well as differences among series, were evaluated by repeated measurement analysis of variance and Tukey's multiple comparison test.

### Results

Values for all animals without pneumoperitoneum were stable in all three series and were therefore grouped into one control group. In control animals anesthesia and ventilation did not cause major changes in PETCO<sub>2</sub>, arterial pCO<sub>2</sub>, and pH. The 70% FiO<sub>2</sub> caused a pO<sub>2</sub> increase from 95 to 100 to 350 mm Hg. No obvious changes were seen for sO<sub>2</sub>, p50, O<sub>2</sub>Hb, and RHb concentrations, or for HCO<sub>3</sub>, ABE, SBE, SBC, and lactate concentrations, (Figures 1 and 2).

In series I and II, CO<sub>2</sub> pneumoperitoneum was associated with pronounced and progressively increasing carboxemia, as evidenced by elevated PETCO<sub>2</sub>



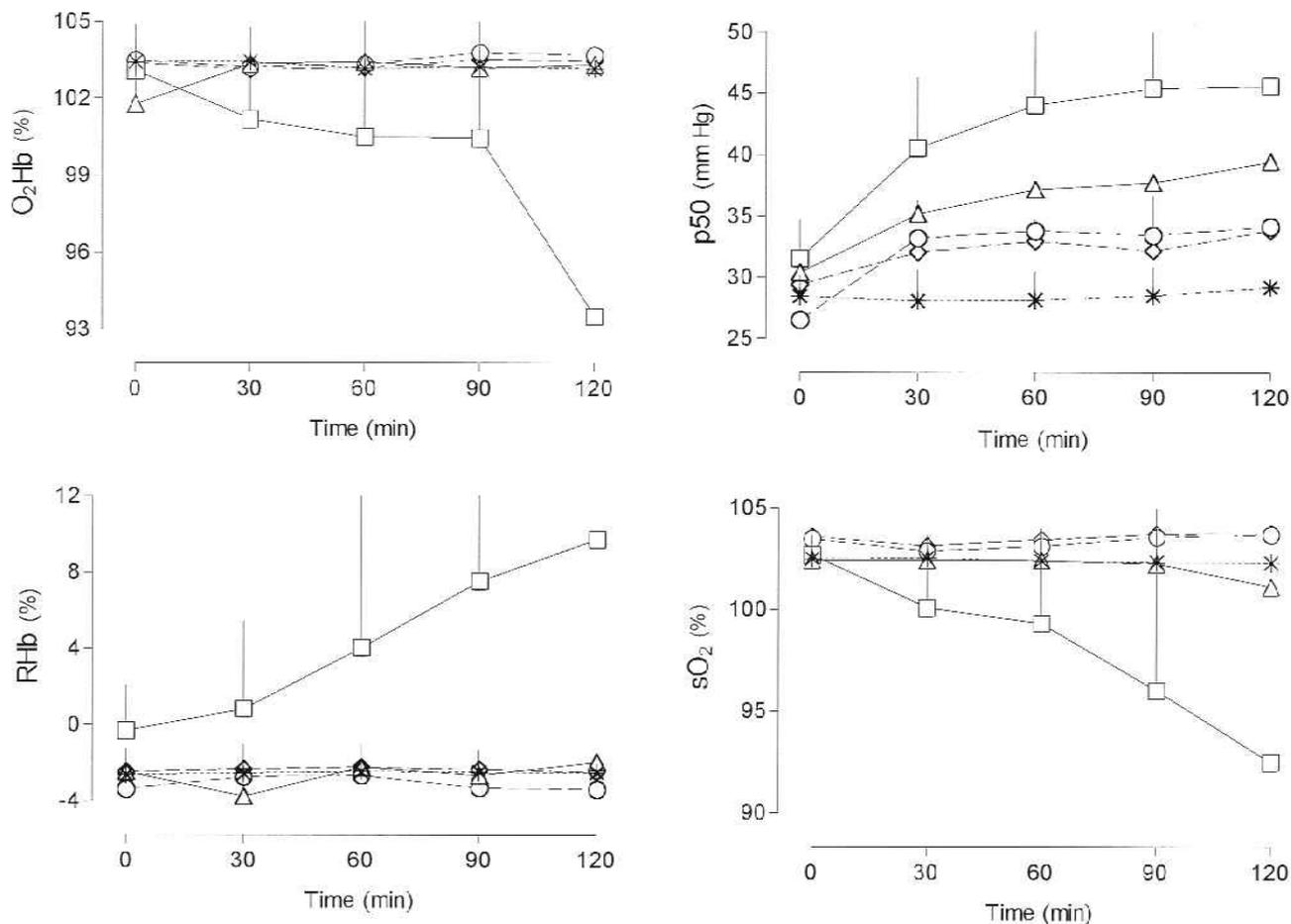
**FIGURE 1.** Effect of CO<sub>2</sub> pneumoperitoneum and insufflation pressure on blood gases and acid-base homeostasis in control rabbits without pneumoperitoneum (control \*—\*), spontaneously breathing animals (series I —△—), superficially ventilated animals (series II —□—), and optimally ventilated animals with insufflation pressures of 10 mm Hg (series IIIA —○—) or 6 mm Hg (series IIIB —◇—). Values are means ± SD.

(not shown) and pCO<sub>2</sub> (both series p <0.001). This CO<sub>2</sub> accumulation caused acidemia, which was initially respiratory acidosis and later metabolic acidosis, as shown by progressively decreasing pH (both series p <0.001) and increased concentrations of lactate (not shown) and HCO<sub>3</sub><sup>-</sup> (control vs series I p <0.05, series II p <0.01). Carboxemia also caused changes in acid-base balance as manifested by progressively increasing deficiency of ABE (control vs series II p <0.001) and SBE, and decrease of SBC (not shown). At the same time sO<sub>2</sub> (control vs series II p <0.01) and concentration of O<sub>2</sub>Hb decreased (control vs series II p <0.05), whereas p50 (both series p <0.001) and concentration of RHb (control vs series II p <0.001) increased. The pO<sub>2</sub> and tO<sub>2</sub> (not shown)

also decreased at the end of the experiment. These effects were most pronounced in series II (vs series I pH, RHb, and p50 p <0.001; sO<sub>2</sub> p <0.01; pCO<sub>2</sub> and O<sub>2</sub>Hb p <0.05).

In animals with optimal ventilation and 10-mm Hg insufflation pressure (series IIIA) the effects of CO<sub>2</sub> pneumoperitoneum were similar (vs control pCO<sub>2</sub> p <0.01; pH and p50 p <0.001), but less pronounced (vs series I p50 p <0.01; vs series II pCO<sub>2</sub>, pH, ABE, RHb, p50, and sO<sub>2</sub> p <0.001; O<sub>2</sub> Hb <0.05), without metabolic acidosis (vs control HCO<sub>3</sub><sup>-</sup> and ABE p >0.05) and hypoxemia (vs control O<sub>2</sub>Hb, RHb, and sO<sub>2</sub> p >0.05).

The effects were even less pronounced in animals with lower (6 mm Hg) insufflation pressure (vs



**FIGURE 2.** Effect of CO<sub>2</sub> pneumoperitoneum and insufflation pressure on blood oximetry and oxygen status in control rabbits without pneumoperitoneum (control \*), spontaneously breathing animals (series I  $\triangle$ ), superficially ventilated animals (series II  $\square$ ), and optimally ventilated animals with insufflation pressures of 10 mm Hg (series IIIA  $\circ$ ) or 6 mm Hg (series IIIB  $\diamond$ ). Values are means  $\pm$  SD.

control pH and p50  $p < 0.001$ ; vs series I pCO<sub>2</sub>  $p < 0.05$ ; pH  $p < 0.01$ , p50  $p < 0.001$ ; vs series II pCO<sub>2</sub>, pH, ABE, RHb, sO<sub>2</sub>, and p50  $p < 0.001$ ; O<sub>2</sub>Hb  $p < 0.05$ ; that is, slight carboxemia with moderately increased arterial pCO<sub>2</sub> (vs control and series IIIA  $p > 0.05$ ), tCO<sub>2</sub> (not shown), and slight respiratory acidosis with moderately decreasing pH (vs series IIIA  $p > 0.05$ ), without metabolic acidosis (vs control HCO<sub>3</sub> and ABE  $p > 0.05$ ) and hypoxemia (vs control O<sub>2</sub>Hb, RHb, and sO<sub>2</sub>  $p > 0.05$ ), see Table 1.

## Discussion

Changes in blood gases and acid-base balance during anesthesia and CO<sub>2</sub> pneumoperitoneum are well

investigated in humans and in experimental studies in large animals. Although rabbits are frequently used in ventilation experiments,<sup>26,27</sup> the effects of pneumoperitoneum are poorly documented<sup>29</sup> and to the best of our knowledge, our data constitute the first complete evaluation of arterial blood gases in anesthetized and ventilated rabbits<sup>25</sup> during pneumoperitoneum.

During anesthesia and CO<sub>2</sub> pneumoperitoneum most authors describe carboxemia and acidosis rapidly reaching a plateau after 15, 30, and 40 minutes in dogs,<sup>15</sup> rabbits,<sup>29</sup> and pigs,<sup>30</sup> respectively. In addition, higher insufflation pressures and limited cardiovascular and/or respiratory adaptation aggravate these changes in blood gases and acid-base homeostasis, phenomena that become especially important during

**TABLE 1. Probability Values among Control and CO<sub>2</sub> Pneumoperitoneum (spontaneously breathing animals, series I), Superficially Ventilated Animals (series II), and Optimally Ventilated Animals with Insufflation Pressures of 10 mm Hg (series IIIA) or 6 mm Hg (series IIIB)**

Assays	Control vs				Series I vs			Series II vs		Series IIIA vs
	Series I	Series II	Series IIIA	Series IIIB	Series II	Series IIIA	Series IIIB	Series IIIA	Series IIIB	Series IIIB
pCO <sub>2</sub>	0.001	0.001	0.01	NS	0.05					
pH	0.001	0.001	0.001	0.001	0.001	NS	0.01	0.001	0.001	NS
HCO <sub>3</sub>	0.05	0.01	NS	NS	NS	NS	NS	NS	NS	NS
ABE	NS	0.001	NS	NS	0.001	NS	NS	0.001	0.001	NS
O <sub>2</sub> Hb	NS	0.05	NS	NS	0.05	NS	NS	0.05	0.05	NS
RHb	NS	0.001	NS	NS	0.001	NS	NS	0.001	0.001	NS
p50	0.001	0.001	0.001	0.001	0.001	0.01	0.001	0.001	0.001	NS
sO <sub>2</sub>	NS	0.01	NS	NS	0.01	NS	NS	0.001	0.001	NS

pCO<sub>2</sub> = partial pressure of carbon dioxide; HCO<sub>3</sub> = hydrogen carbonate; ABE = actual base excess; O<sub>2</sub>Hb = oxyhemoglobin; RHb = reduced hemoglobin; p50 = oxygen tension at half saturation assessing hemoglobin oxygen affinity; sO<sub>2</sub> = oxygen saturation; NS = not significant.

long surgical procedures. The final result depends on the balance between the possibility of correction by ventilation and infusion therapy, and individual patient characteristics such as obesity, degree of Trendelenburg position, duration of surgery, and decreased cardiovascular or ventilation capacity (e.g., by smoking).

In the pathophysiology of CO<sub>2</sub> pneumoperitoneum-induced changes, carboxemia and acidosis are the first and key events (Figure 3), reflected in increases in pCO<sub>2</sub>, PETCO<sub>2</sub>,<sup>29</sup> and HCO<sub>3</sub>, and in a decrease in pH.<sup>31,32</sup> These changes can lead to metabolic acidosis as reflected in increases of PETCO<sub>2</sub>, pCO<sub>2</sub>, tCO<sub>2</sub>, HCO<sub>3</sub>, and lactate, and decreases in pH, ABE, SBE, and SBC. Our data suggest, in addition, metabolic hypoxemia reflected in increases in RHb and p50 and in decreases in pO<sub>2</sub>, tO<sub>2</sub>, and O<sub>2</sub>Hb. This leads to decreases in oxygen saturation and O<sub>2</sub> availability to tissues because of decreased O<sub>2</sub>Hb and hemoglobin oxygen affinity, and an increase in RHb. To the best of our knowledge, this has not been reported before. This observation is consistent with desaturation during diagnostic laparoscopy in patients with liver disease<sup>33</sup> and with acute hypoxemia in a patient with sickle cell hemoglobinopathy.<sup>34</sup> It can be explained by decreased hemoglobin oxygen affinity and by increased abnormal hemoglobin concentration and acidosis.

According to the Bohr effect, oxygen diffusion from erythrocytes to tissue is influenced by pH. Changes in blood gases and in acid-base homeostasis

are therefore accompanied by changes in oxygen metabolism, which can be considered metabolic hypoxemia. Decreased oxygen availability to tissues then results in anaerobic metabolism (glucose → pyruvic acid → lactic acid + 2 adenosine triphosphate), which is confirmed by increased lactate concentrations.

The degree of metabolic acidosis and hypoxia crucially depend, as expected, on ventilation and insufflation pressure. In our experiments the effects were much less pronounced in optimally ventilated animals, in contrast with superficially ventilated animals, in which profound changes were seen. Changes in spontaneously breathing animals were slightly less pronounced than in superficially ventilated animals, but much more than during optimal ventilation. In animals with lower insufflation pressure these effects were minimal.

The clinical importance of these data, besides ventilation and infusion therapy during anesthesia, could relate to adhesion formation<sup>9-12,35</sup> and postoperative pain.<sup>36</sup> Indeed, we described CO<sub>2</sub> pneumoperitoneum-induced mesothelial hypoxia as a cofactor in adhesion formation,<sup>11,12</sup> which increases with time,<sup>9,11</sup> and insufflation pressure,<sup>10</sup> and can be prevented by adding small amounts of oxygen.<sup>10-12,35</sup> The data presented extend the concept of mesothelial hypoxia by introducing the concept of metabolic hypoxemia, not only in superficial layers of peritoneum but also in splanchnic organs.

Fig. 3

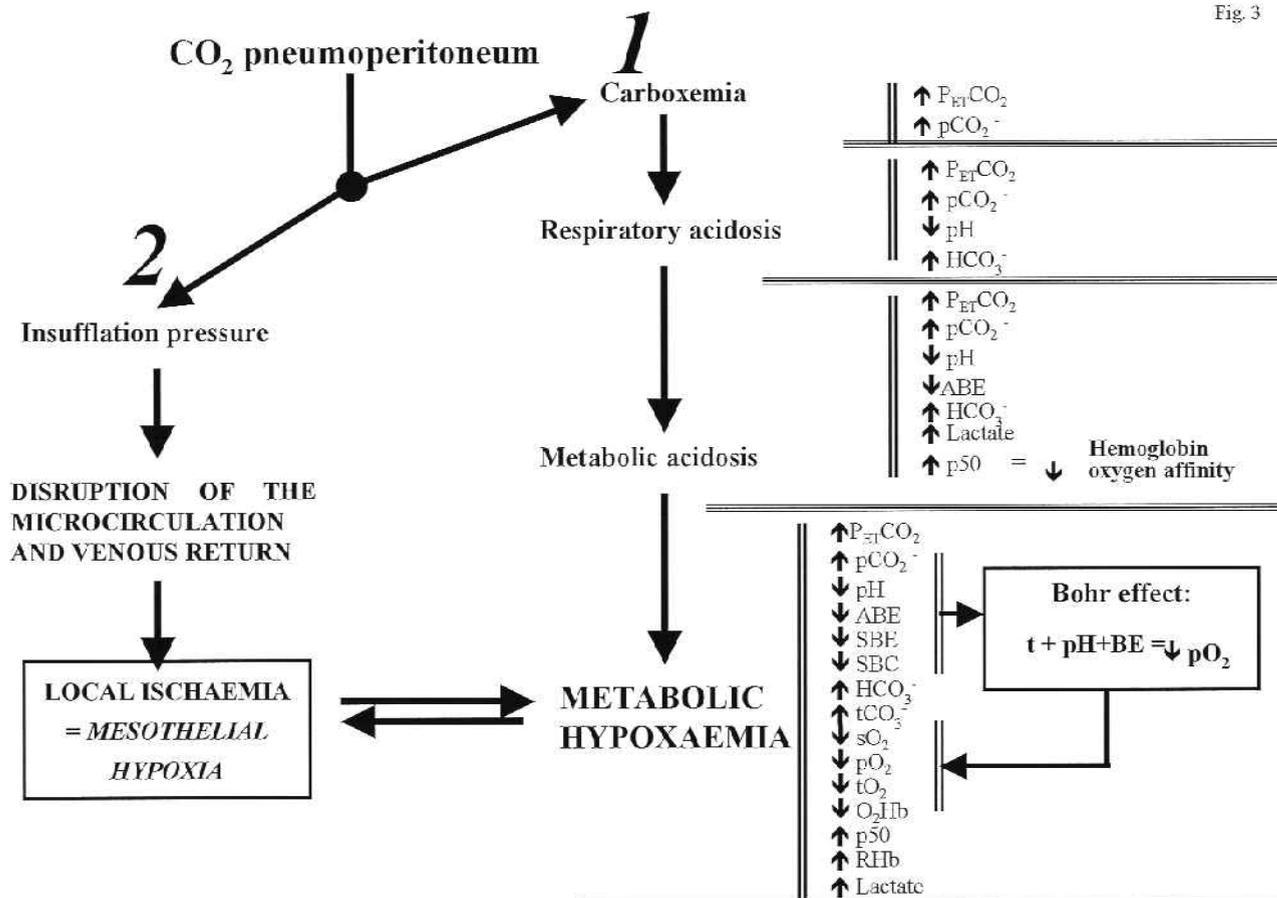


FIGURE 3. Pathogenesis of CO<sub>2</sub> pneumoperitoneum-induced carboxemia, acidemia, acidosis, and mesothelial and splanchnic ischemia, leading to metabolic hypoxemia.

In conclusion, CO<sub>2</sub> pneumoperitoneum causes carboxemia, acidemia, acidosis, and base deficiency, and in addition, changes in oxygen metabolism, which can be considered metabolic hypoxemia.<sup>25</sup> It leads to decreased oxygen availability to tissues, resulting in anaerobic metabolism. This could be important for local ischemia in superficial mesothelial layers of peritoneum and in splanchnic organs, resulting in adhesion formation.<sup>9-12,35</sup>

**References**

1. Baraka A, Jabbour S, Hammoud R, et al: End-tidal carbon dioxide tension during laparoscopic cholecystectomy. Correlation with the baseline value prior to carbon dioxide insufflation. *Anaesthesia* 49:304-306, 1994

2. Lister DR, Rudston-Brown B, Warriner CB, et al: Carbon dioxide absorption is not linearly related to intra-peritoneal carbon dioxide insufflation pressure in pigs. *Anesthesiology* 80:129-136, 1994

3. Liem TK, Krishnamoorthy M, Applebaum H, et al: A comparison of the hemodynamic and ventilatory effects of abdominal insufflation with helium and carbon dioxide in young swine. *J. Pediatr Surg* 31:297-300, 1996

4. Dubecz S Jr, Pianim N, Se-Yuan L, et al: Laparoscopic surgery with carbon dioxide insufflation causes respiratory acidosis. *Acta Chir Hung* 33:93-100, 1992

5. Koster S, Spacek Z, Paweletz N, et al: A scanning microscopy study of the peritoneum in mice after application of a CO<sub>2</sub>-pneumoperitoneum. *Zentralbl Gynakol* 121:244-247, 1999

6. Garner R, Wright E, Ott D: Loss of cell viability due to CO<sub>2</sub> pneumoperitoneum during laparoscopy and maintenance of cell viability at laparoscopy by hydration of CO<sub>2</sub> [abstr]. *J Am Assoc Gynecol Laparosc* 7:S19, 2000
7. Knolmayer TJ, Bowyer MW, Egan JC, et al: The effects of pneumoperitoneum on gastric blood flow and traditional hemodynamic measurements. *Surg Endosc* 12:115–118, 1998
8. Kotzampassi K, Paramythiotis D, Eleftheriadis E: Deterioration of visceral perfusion caused by intra-abdominal hypertension in pigs ventilated with positive end-expiratory pressure. *Surg Today* 30:987–992, 2000
9. Yesildaglar N, Ordonez JL, Laermans I, et al: The mouse as a model to study adhesion formation following endoscopic surgery: A preliminary report. *Hum Reprod* 14:55–59, 1999
10. Yesildaglar N, Koninckx PR: Adhesion formation in intubated rabbits increases with high insufflation pressure during endoscopic surgery. *Hum Reprod* 15:687–691, 2000
11. Molinas CR, Koninckx PR: Hypoxaemia induced by CO<sub>2</sub> or helium pneumoperitoneum is a co-factor in adhesion formation in rabbits. *Hum Reprod* 15:1758–1763, 2000
12. Molinas CR, Mynbaev OA, Pauwels A, et al: Peritoneal mesothelial hypoxia during pneumoperitoneum is a cofactor in adhesion formation in a laparoscopic mouse model. *Fertil Steril* 176:560–567, 2001
13. Mathew G, Watson DI, Ellis TS, et al: The role of peritoneal immunity and the tumour-bearing state on the development of wound and peritoneal metastases after laparoscopy. *Aust N Z J Surg* 69:14–18, 1999
14. Canis M, Botchorishvili R, Wattiez A, et al: Tumor growth and dissemination after laparotomy and CO<sub>2</sub> pneumoperitoneum: A rat ovarian cancer model. *Obstet Gynecol* 92:104–108, 1998
15. Kotzampassi K, Kapanidis N, Kazamias P, et al: Hemodynamic events in the peritoneal environment during pneumoperitoneum in dogs. *Surg Endosc* 7:494–499, 1993
16. Berg K, Wilhelm W, Grundmann U, et al: Laparoscopic cholecystectomy—Effect of position changes and CO<sub>2</sub> pneumoperitoneum on hemodynamic, respiratory and endocrinologic parameters. *Zentralbl Chir* 122:395–404, 1997
17. Donaldson LL, Trostle SS, White NA: Cardiopulmonary changes associated with abdominal insufflation of carbon dioxide in mechanically ventilated, dorsally recumbent, halothane anaesthetised horses. *Equine Vet J* 30:144–151, 1998
18. Wittgen CM, Andrus CH, Fitzgerald SD, et al: Analysis of the hemodynamic and ventilatory effects of laparoscopic cholecystectomy. *Arch Surg* 126:997–1000, 1991
19. Hoka S, Arimura H, Bosnjak ZJ, et al: Regional venous outflow, blood volume, and sympathetic nerve activity during hypercapnia and hypoxic hypercapnia. *Can J Physiol Pharmacol* 70:1032–1039, 1992
20. Joris JL, Chiche JD, Canivet JL, et al: Hemodynamic changes induced by laparoscopy and their endocrine correlates: Effects of clonidine. *J Am Coll Cardiol* 32:1389–1396, 1998
21. Myre K, Rostrup M, Buanes T, et al: Plasma catecholamines and haemodynamic changes during pneumoperitoneum. *Acta Anaesthesiol Scand* 42:343–347, 1998
22. Taura P, Lopez A, Lacy AM, et al: Prolonged pneumoperitoneum at 15 mm Hg causes lactic acidosis. *Surg Endosc* 12:198–201, 1998
23. Demers P, Ratelle R, Boudreault D, et al: Comparison of hemodynamic and ventilatory effects of pneumoperitoneum using carbon dioxide or abdominal suspension during laparoscopic cholecystectomy. *Ann Chir* 50:593–600, 1996
24. Shuto K, Kitano S, Yoshida T, et al: Hemodynamic and arterial blood gas changes during carbon dioxide and helium pneumoperitoneum in pigs. *Surg Endosc* 9:1173–1178, 1995
25. Mynbaev OA, Molinas CR, Vanacker B, et al: Metabolic effect of the addition of 6% O<sub>2</sub> to the CO<sub>2</sub>–pneumoperitoneum [abstr]. *Hum Reprod* 16:61, 2001
26. Kerr CL, Veldhuizen RAW, Lewis JF: Effects of high-frequency oscillation on endogenous surfactant in an acute lung injury model. *Am J Respir Crit Care Med* 164(2):237–242, 2001
27. Mols G, Hermle G, Schubert J, et al: Volume-dependent compliance and ventilation-perfusion mismatch in surfactant-depleted isolated rabbit lungs. *Crit Care Med* 29(1):144–151, 2001

28. Steinman M, da Silva LE, Coelho IJC, et al: Hemodynamic and metabolic effects of CO<sub>2</sub> pneumoperitoneum in an experimental model of hemorrhagic shock due to retroperitoneal hematoma. *Surg Endosc* 12:416–420, 1998
29. Portilla E, Garcia D, Rodriguez-Reynoso S, et al: Arterial blood gas changes in New Zealand white rabbits during carbon dioxide-induced pneumoperitoneum. *Lab Anim Sci* 48:398–400, 1998
30. Davidson BS, Cromeens DM, Feig BW: Alternative methods of exposure minimize cardiopulmonary risk in experimental animals during minimally invasive surgery. *Surg Endosc* 10:301–304, 1996
31. Corsale I, Fantini C, Gentili C, et al: Peritoneal innervation and post-laparoscopic course. Role of CO<sub>2</sub>. *Minerva Chir* 55:205–210, 2000
32. Kuntz C, Wunsch A, Bodeker C, et al: Effect of pressure and gas type on intraabdominal, subcutaneous, and blood pH in laparoscopy. *Surg Endosc* 14:367–371, 2000
33. Haydon GH, Dillon J, Simpson KJ, et al: Hypoxemia during diagnostic laparoscopy: A prospective study. *Gastrointest. Endosc.* 44:124–128, 1996
34. Cunningham AJ: Anesthetic implications of laparoscopic surgery. *Yale J Biol Med* 71:551–578, 1999
35. Koninckx PR: Laparoscopy and adhesions: What role for hypoxemia? Presented at the expert conference of the European Society for Gynaecological Endoscopy, Clermont-Ferrand, France, October 18, 2000
36. Jackson SA, Laurence AS, Hill JC: Does post-laparoscopy pain relate to residual carbon dioxide? *Anaesthesia* 51:485–487, 1996