Pathogenesis of CO_2 Pneumoperitoneum-Induced Metabolic Hypoxemia in a Rabbit Model

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Abstract

Study Objective. *To investigate the effects of carbon dioxide (CO_2) 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_2 pneumoperitoneum profoundly affected blood gases, acid-base balance, and oxygen homeostasis. Carboxemia with increasing end-tidal CO_2 and partial pressure of CO_2 ($p < 0.001$), 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_2 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.*

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Pneumoperitoneum is essential to perform endoscopic surgical procedures in the abdominal cavity. Carbon dioxide (CO_2) 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[1–3] and controlled by ventilation.[2,4]

The CO_2 pneumoperitoneum has local effects on peritoneum either directly or through desiccation or cooling. It is painful under local anesthesia. Disruption of morphologic integrity[5] can largely be prevented by humidification.[6] Changes in gastric and small bowel intramucosal pH[7,8] are probably direct effects of CO_2 pneumoperitoneum. Increased postoperative adhesions are known to be a direct effect.[9–12] It is unclear to what extent changes in microcirculation,[8] macrophage and immune function,[13] and tumor growth[13,14] can be prevented by humidification and warming.

Blood gases and acid-base balance change during CO_2 pneumoperitoneum,[1–4] with hypercarbia, acidemia, acidosis, and hypoxemia. Arterial and venous partial pressures of CO_2 (pCO_2) increase,[2,4,15] and arterial and mixed venous pH,[16,17] O_2 saturation (sO_2), and arterial pO_2 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.[18] During anesthesia, however, effects of CO_2 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_2.

Effects induced by CO_2 pneumoperitoneum such as hypercarbia and hypoxia are associated with increasing sympathetic activity from a variety of subcortical centers.[19] Pneumoperitoneum also increases plasma concentrations of vasopressin, cortisol, and catecholamines such as noradrenaline, epinephrine, and norepinephrine.[16,20–22] The systemic effect of these substances is associated with changes in function in cardiovascular, respiratory, and urinary systems. A CO_2 pneumoperitoneum increases minute ventilation and peak inspiratory pressure,[23] pulmonary vascular resistance,[20] alveolar CO_2 concentration, calculated physiologic shunt,[17] central venous pressure, systolic and diastolic arterial pressures, and systemic vascular resistance,[16, 20] and reduces liver and renal blood flow and urinary output.[24] During anesthesia in the human, these effects are reduced by adequate hyperventilation and infusion therapy.

Since we demonstrated local effects of CO_2 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_2.[25] A prerequisite for this study was evaluation in the rabbit of the effect of ventilation parameters and pneumoperitoneum pressures on CO_2 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 administrated 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_2) 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.[26,27] Respiratory rates were adjusted during pilot experiments to obtain baseline arterial pCO_2 lower than 45 mm Hg as described elsewhere.[3,28]

Pulse rate and sO_2 (in %) in peripheral blood (ear vessels, capillaries), end-tidal CO_2 ($P_{ET}CO_2$), 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 Thermoflotar Plus (Karl Storz, Tüttlingen, 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_2, a continuous flow rate through the abdominal cavity of 80 ml/minute was used to remove constantly any O_2 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_2 causes minimal desiccation.[10] 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_2, and pCO_2; blood oximetry values such as sO_2, oxyhemoglobin (O_2Hb), and reduced hemoglobin (RHb); oxygen status values such as total oxygen concentration (tO_2) and oxygen tension at half saturation assessing the hemoglobin oxygen affinity (p50); and acid-base values such as concentrations of hydrogen carbonate (HCO_3), standard bicarbonate (SBC), actual base excess (ABE), standard base excess (SBE), and concentration of total carbon dioxide (tCO_2). 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_2 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 $P_{ET}CO_2$, arterial pCO_2, and pH. The 70% FiO_2 caused a pO_2 increase from 95 to 100 to 350 mm Hg. No obvious changes were seen for sO_2, p50, O_2Hb, and RHb concentrations, or for HCO_3, ABE, SBE, SBC, and lactate concentrations, (Figures 1 and 2).

In series I and II, CO_2 pneumoperitoneum was associated with pronounced and progressively increasing carboxemia, as evidenced by elevated $P_{ET}CO_2$

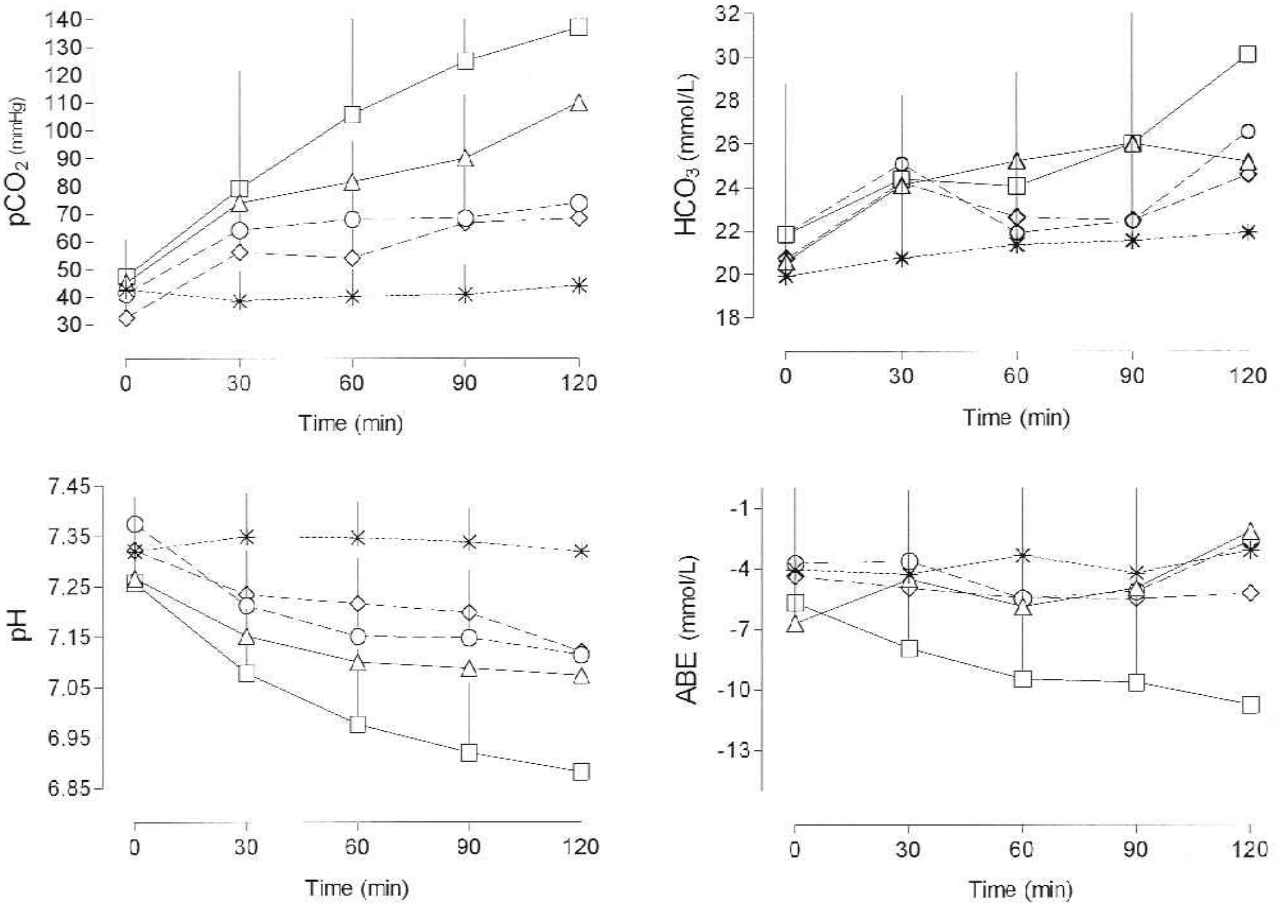

FIGURE 1. Effect of CO_2 pneumoperitoneum and insufflation pressure on blood gases and acid-base homeostasis in control rabbits without pneumoperitoneum (control ···✳···), spontaneously breathing animals (series I —△—), superficially ventilated animals (series II —□—), and optimally ventilated animals with insufflation pressures of 10 mm Hg (series IIIA —○—) or 6 mm Hg (series IIIB —◇—). Values are means ± SD.

(not shown) and pCO_2 (both series $p < 0.001$). This CO_2 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_3 (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_2 (control vs series II $p < 0.01$) and concentration of O_2Hb 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_2 and tO_2 (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_2 $p < 0.01$; pCO_2 and O_2Hb $p < 0.05$).

In animals with optimal ventilation and 10-mm Hg insufflation pressure (series IIIA) the effects of CO_2 pneumoperitoneum were similar (vs control pCO_2 $p < 0.01$; pH and p50 $p < 0.001$), but less pronounced (vs series I p50 $p < 0.01$; vs series II pCO_2, pH, ABE, RHb, p50, and sO_2 $p < 0.001$; O_2 Hb<0.05), without metabolic acidosis (vs control HCO_3^- and ABE $p > 0.05$) and hypoxemia (vs control O_2Hb, RHb, and sO_2 $p > 0.05$).

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

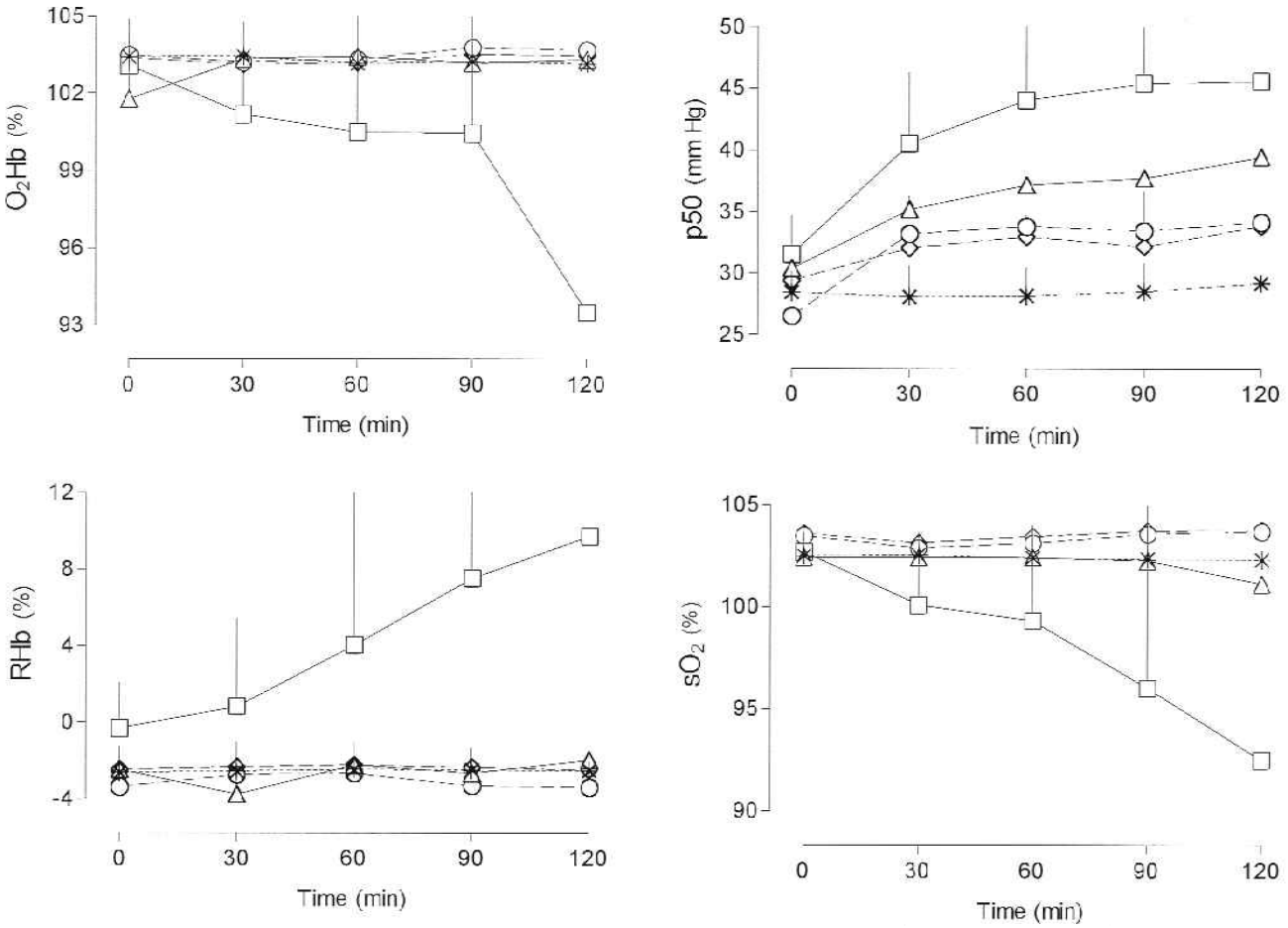

FIGURE 2. Effect of CO_2 pneumoperitoneum and insufflation pressure on blood oximetry and oxygen status in control rabbits without pneumoperitoneum (control ··✳··), spontaneously breathing animals (series I —△—), superficially ventilated animals (series II —□—), and optimally ventilated animals with insufflation pressures of 10 mm Hg (series IIIA —○—) or 6 mm Hg (series IIIB —◇—). Values are means ± SD.

control pH and p50 p <0.001; vs series I pCO_2 p <0.05; pH p <0.01, p50 p <0.001; vs series II pCO_2, pH, ABE, RHb, sO_2, and p50 p <0.001; O_2Hb p <0.05); that is, slight carboxemia with moderately increased arterial pCO_2 (vs control and series IIIA p >0.05), tCO_2 (not shown), and slight respiratory acidosis with moderately decreasing pH (vs series IIIA p >0.05), without metabolic acidosis (vs control HCO_3 and ABE p >0.05) and hypoxemia (vs control O_2 Hb, RHb, and sO_2 p >0.05), see Table 1.

Discussion

Changes in blood gases and acid-base balance during anesthesia and CO_2 pneumoperitoneum are well investigated in humans and in experimental studies in large animals. Although rabbits are frequently used in ventilation experiments,[26,27] the effects of pneumoperitoneum are poorly documented[29] and to the best of our knowledge, our data constitute the first complete evaluation of arterial blood gases in anesthetized and ventilated rabbits[25] during pneumoperitoneum.

During anesthesia and CO_2 pneumoperitoneum most authors describe carboxemia and acidosis rapidly reaching a plateau after 15, 30, and 40 minutes in dogs,[15] rabbits,[29] and pigs,[30] 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_2 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)

	Control vs				Series I vs			Series II vs		Series IIIA vs
Assays	Series I	Series II	Series IIIA	Series IIIB	Series II	Series IIIA	Series IIIB	Series IIIA	Series IIIB	Series IIIB
pCO_2	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_3	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_2Hb	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_2	NS	0.01	NS	NS	0.01	NS	NS	0.001	0.001	NS

pCO_2 = partial pressure of carbon dioxide; HCO_3 = hydrogen carbonate; ABE = actual base excess; O_2Hb = oxyhemoglobin; RHb = reduced hemoglobin; p50 = oxygen tension at half saturation assessing hemoglobin oxygen affinity; sO_2 = 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_2 pneumoperitoneum-induced changes, carboxemia and acidosis are the first and key events (Figure 3), reflected in increases in pCO_2, $P_{ET}CO_2$,[29] and HCO_3, and in a decrease in pH.[31,32] These changes can lead to metabolic acidosis as reflected in increases of $P_{ET}CO_2$, pCO_2, tCO_2, HCO_3, 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_2, tO_2, and O_2Hb. This leads to decreases in oxygen saturation and O_2 availability to tissues because of decreased O_2Hb 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[33] and with acute hypoxemia in a patient with sickle cell hemoglobinopathy.[34] 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[9–12,35] and postoperative pain.[36] Indeed, we described CO_2 pneumoperitoneum-induced mesothelial hypoxia as a cofactor in adhesion formation,[11,12] which increases with time,[9,11] and insufflation pressure,[10] and can be prevented by adding small amounts of oxygen.[10–12,35] 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.

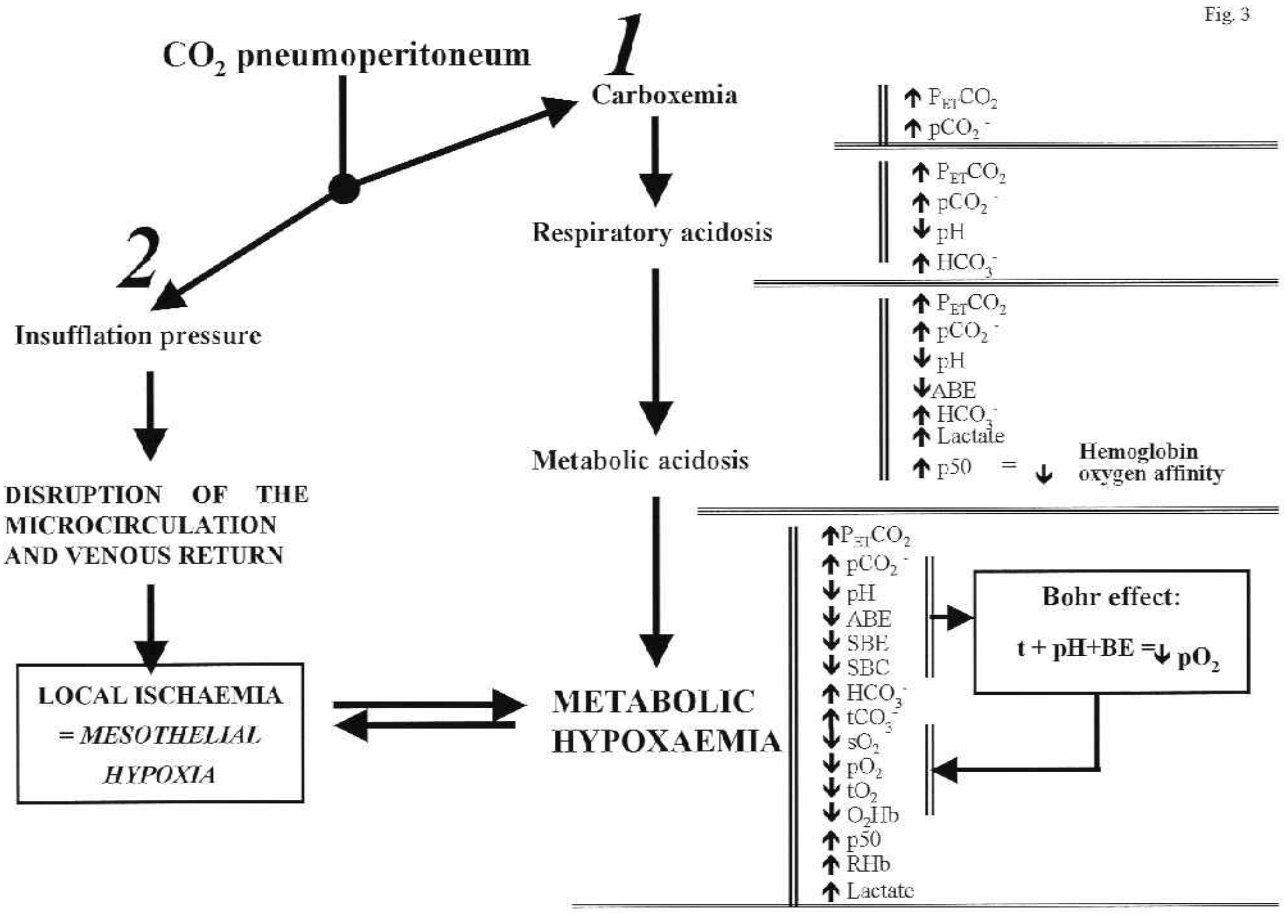

FIGURE 3. Pathogenesis of CO_2 pneumoperitoneum-induced carboxemia, acidemia, acidosis, and mesothelial and splanchnic ischemia, leading to metabolic hypoxemia.

In conclusion, CO_2 pneumoperitoneum causes carboxemia, acidemia, acidosis, and base deficiency, and in addition, changes in oxygen metabolism, which can be considered metabolic hypoxemia.[25] 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.[9–12,35]

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