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Reduction of CO_2-pneumoperitoneum-induced metabolic hypoxaemia by the addition of small amounts of O_2 to the CO_2 in a rabbit ventilated model. A preliminary study

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BACKGROUND: CO_2-pneumoperitoneum used in endoscopic surgery induces system effects by CO_2 absorption. This study investigated the effect of the addition of O_2 to CO_2-pneumoperitoneum, upon CO_2 absorption. METHODS: The effect of a pneumoperitoneum using 100% CO_2 or 94% CO_2 + 6% O_2 upon arterial blood gases, acid base and O_2 homeostasis was evaluated. In series A suboptimal ventilation and a pneumoperitoneum pressure (PP) of 10 mmHg was used. In series B adequate ventilation and PP of 6 mmHg was used. RESULTS: CO_2-pneumoperitoneum profoundly affected blood gases and acid base homeostasis i.e. increasing pCO_2, HCO_3 ($P < 0.001$) and lactate concentrations ($P < 0.05$) and decreasing pH, actual base excess and standard bicarbonate ($P < 0.001$), resulting in metabolic hypoxaemia with desaturation, lower pO_2 ($P < 0.001$) and O_2Hb ($P < 0.05$). These effects were more pronounced with higher PP and suboptimal ventilation. CONCLUSION: CO_2-pneumoperitoneum profoundly affected blood gases and acid base homeostasis resulting in metabolic hypoxaemia. The addition of 6% of O_2 to the CO_2-pneumoperitoneum prevented these effects to a large extent. If these preliminary data are confirmed in the human, the addition of a few percent of O_2 to CO_2 could become important for endoscopic surgery of long duration, especially in obese patients with limited cardiorespiratory adaptation and steep Trendelenburg.

Key words: acidosis/carboxaemia/CO_2-pneumoperitoneum/metabolic hypoxaemia/oxygen

Introduction

Endoscopic surgery is associated with less postoperative pain, lower morbidity, shorter hospitalization, better cosmetic results and a faster return to normal activities. CO_2 is generally used for the pneumoperitoneum for safety reasons because of its high solubility in water and its high exchange capacity in the lungs. The concentration of CO_2 can moreover easily be monitored by capnography and controlled by ventilation (Wright *et al.*, 1995; Gebhardt *et al.*, 1997).

CO_2-pneumoperitoneum induces systemic effects by CO_2 absorption, and by the intraperitoneal pressure which affects venous return (Kotzampassi *et al.*, 1993). Firstly, CO_2 absorption increases the end tidal CO_2, arterial pCO_2 and mixed venous pCO_2 (Kotzampassi *et al.*, 1993; Gandara *et al.*, 1997). This carboxaemia induces a respiratory and metabolic acidosis, decreasing both arterial and mixed venous pH and arterial pO_2 (Liem *et al.*, 1996; Gandara *et al.*, 1997; Gebhardt *et al.*, 1997; Knolmayer *et al.*, 1998). CO_2 absorption negatively affects respiratory function (Junghans *et al.*, 1997) an effect not observed by inert gases such as helium and argon. Minute ventilation, peak inspiratory pressure, pulmonary vascular resistance, alveolar CO_2 concentration, calculated physiological shunt, central venous pressure, systolic and diastolic arterial pressure and systemic vascular resistance and the cardiac output are increased (Kotzampassi *et al.*, 1993; Gebhardt *et al.*, 1997; Knolmayer *et al.*, 1998). These effects of CO_2 absorption are more pronounced in those patients with limited pulmonary or cardiovascular adaptation (Gebhardt *et al.*, 1997) with liver or blood disease (Cunningham and Schlanger, 1992; Haydon *et al.*, 1996) and also with long duration of endoscopic surgery and steep Trendelenburg (Stone *et al.*, 1998). Higher intraperitoneal pressures are associated with a reduction of visceral blood flow and urinary output (Caldwell and Ricotta, 1987; Kotzampassi *et al.*, 1993). In rats the portal blood flow linearly decreases with intraperitoneal pressures of 2–12 mmHg affecting hepatic function and cellular immunity (Gutt and

Schmandra, 1999). In pigs the femoral vein collapses with a pressure of 20–30 mmHg (Bazin *et al.*, 1997).

CO_2-pneumoperitoneum also has local effects. CO_2-pneumoperitoneum decreases the peritoneal pH (Corsale *et al.*, 2000), morphological integrity (Koster *et al.*, 1999) and visceral microcirculation (Caldwell and Ricotta, 1987). It decreases the gastric and intestinal intramucosal pH and affects the hepatic, gastric and intestinal microcirculation (Caldwell and Ricotta, 1987; Kotzampassi *et al.*, 1993; Knolmayer *et al.*, 1998). CO_2-pneumoperitoneum is also a co-factor in adhesion formation. In rabbits and mice adhesions increase with duration and pressure of the CO_2-pneumoperitoneum (Yesildaglar *et al.*, 1999, 2000; Molinas and Koninckx, 2000; Molinas *et al.*, 2001). This increase in adhesions can be prevented by the addition of small amounts of O_2 to the CO_2-pneumoperitoneum, suggesting local mesothelial hypoxia as a mechanism (Koninckx, 2000; Molinas *et al.*, 2001). Since these local effects of the addition of small amounts of O_2 were so pronounced, the systemic effects of adding small amounts of O_2 to the CO_2-pneumoperitoneum were investigated in a rabbit model.

Materials and methods

Animals

Adult female New Zealand white rabbits ($n = 20$) weighing between 2.7 and 3.0 kg were used. They were kept under standard laboratory conditions at a temperature of 20–25°C, and a relative humidity of 40–70%. They had a day cycle of 14 h light and 10 h 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 (Animalium, St Rafael Hospital. K.U.Leuven, Belgium) and the experiments were approved by The Institutional Review Animal Care Committee.

The animals were premedicated with an i.m. injection of 30 mg/kg Ketamine 1000 (Sanofi®; Sante Animale Benelux, Brussels, Belgium) and 6 mg/kg of 2% xylazine hydrochloridum solution (VMD, Arendonk, Belgium). After intubation with a 3.5 mm endotracheal tube (Sheridan Catheter Corp., New York, NY, USA) inhalation anaesthesia was performed with 2.5% halothane (Fluothane®; Zeneca, Destelbergen, Belgium) mixed with O_2 and room air with concentrations of O_2 in inspirated gas fractional inspired O_2 concentration (FiO_2) 0.7, using a vaporizer (Drägerwerk, Lubeck, Germany) connected to a small animal ventilator (Model 683; Harvard Apparatus Inc., Holliston, MA, USA). During anaesthesia the haemodynamic and respiratory parameters were monitored continuously, i.e. pulse rate and O_2 saturation (SpO_2, in %) in the peripheral blood (ear vessels), end tidal CO_2 ($P_{ET}CO_2$) and respiratory pressure, using an electrocardiogram, a blood pressure meter (Hewlett Packard, Boeblingen, Germany), a pulse oximeter (Nellcor, Hayward, CA, USA), a capnograph (Capnomac; Datex, Finland) and a manometer respectively.

Surgical protocol

The animals were placed in the supine position and the abdomen was shaved and disinfected with polyvidone iodine (Iso-Betadine; Asta Medica, Brussels, Belgium). The surgical procedures included a pneumoperitoneum created with a 10 mm trocar (Apple®; Medical Corporation, USA) placed caudally to the sternum. For the pneumoperitoneum the Thermoflotar Plus (Karl Storz, Tüttlingen, Germany) was used with a humidifier (Aquapor; Drägerwerk) and with a heating device (Opti Therm; Karl Storz) keeping the insufflation temperature between 35–37°C. In addition a water valve was used to dampen changes in the insufflation pressure. Taking into account the high exchange capacity of the peritoneum and to maintain a 100% concentration of CO_2, a continuous flow rate through the abdominal cavity of some 80 ml/min was used to constantly remove any O_2, which might have diffused from the circulation. To achieve this a 22 gauge catheter (Insyte-W®; Vialon®; Becton Dickinson, Madrid, Spain) was inserted through the abdominal wall. This flow rate with heated and humidified CO_2 caused hardly any desiccation (Yesildaglar *et al.*, 2000). Insufflation was carried out through the 10 mm trocar inserted superficially.

Experimental design

In superficially and adequately ventilated rabbits a control group without pneumoperitoneum ($n = 4$ and 3 respectively) was compared with animals with a pneumoperitoneum, using either 100% CO_2 ($n = 4$ and 3), or 6% of O_2 + 94% CO_2 ($n = 3$ and 3). In the superficially ventilated (tidal volume of 6.7 ml/kg and a respiratory rate of 27–29 per min) animals (series A) intraperitoneal pressure was 10 mmHg and in the adequately ventilated (tidal volume of 11.3 ml/kg and a respiratory rate of 18–21 per min) animals (series B) intraperitoneal pressure was 6 mmHg. Ventilation (superficially or adequately) and intraperitoneal pressures were chosen as described (Mynbaev *et al.*, 2002). From these experiments the groups with the most and least pronounced effects of CO_2 pneumoperitoneum were chosen to investigate the effect of the addition of 6% of O_2. A concentration of 6% O_2 was chosen since in adhesion prevention studies optimal effects between 2–10% of O_2 were observed (Molinas *et al.*, 2001). For both series of experiments, animals were block randomized by day. In series A, one animal died in the group with 94% CO_2 + 6% O_2.

Assays

The ear artery was catheterized with a 20 gauge catheter (Insyte-W®, Vialon®; Becton Dickinson). The syringes and catheters were rinsed with 0.3 ml of saline with 5 IU heparin/l (Rhône-Poulenc Rorer, Brussels, Belgium). The first sample was taken before starting pneumoperitoneum and the following samples were taken every 30 min for 210 min in series A and every 15 min for 120 min in series B. Syringes with blood samples were put on ice immediately and analysed in duplicate in the blood gas analyser (Ablhm System 625/620; Radiometer, Copenhagen, Denmark). At the end of the experiment the animals were killed with an i.v. injection of 0.3 ml/kg T61 (Intervet, Mechelen, Belgium).

The following values were measured: arterial blood gas parameters such as pH, partial pressures of O_2 (pO_2) and CO_2 (pCO_2); acid base parameters such as concentrations of hydrogen carbonate (HCO_3-), standard bicarbonate (SBC), actual base excess (ABE), standard base excess (SBE) and the concentration of total carbon dioxide (tCO_2); blood oximetry parameters such as O_2 saturation (sO_2), oxihaemoglobin (O_2Hb) and reduced haemoglobin (RHb); O_2 status parameters such as total O_2 concentration (tO_2) and O_2 tension at half saturation assessing the haemoglobin O_2 affinity (p50). Finally the lactate concentration was measured.

Data analysis and statistical methods

Data were analysed using Graph Pad Prism (Graph Pad Software Inc., San Diego, CA, USA). Differences between the three experimental groups in each series were evaluated by repeated measurement ANOVA. Subsequently differences between groups one and two, between groups one and three, and between groups two and three were evaluated by Turkey's multiple comparison tests. Mean ± SEM is given unless stated otherwise.

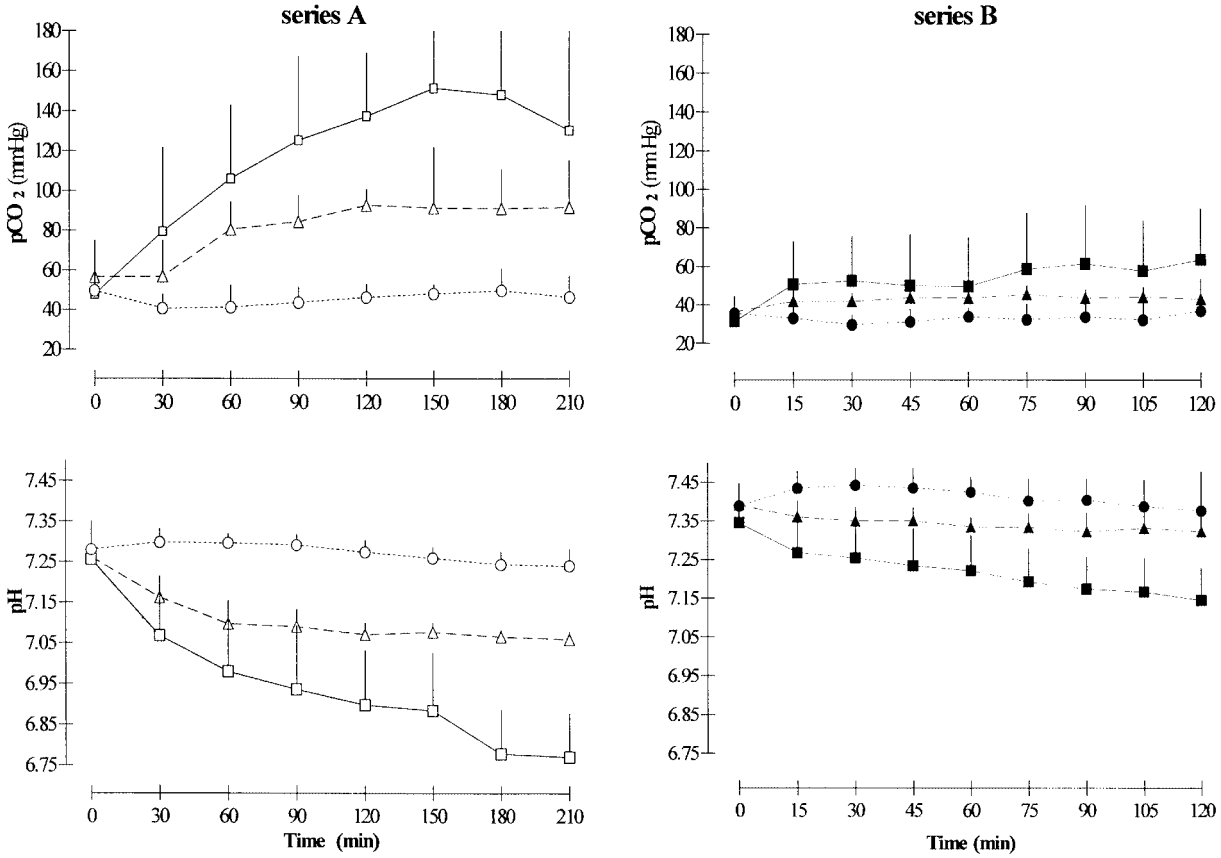

Figure 1. Arterial blood gases (pCO_2 and pH) in rabbits without pneumoperitoneum (group one —◇— and —◆— in series A and B respectively), during pneumoperitoneum with 100% CO_2 (group two —□— and —■— in series A and B respectively) and 6% O_2 + 94% CO_2 (group three —△— and —▲— in series A and B respectively). X: time, min and Y: means ± SD are given.

Results

In both control groups anaesthesia and ventilation alone did not cause major changes in the concentrations of arterial pCO_2 (Figure 1), tCO_2 and $P_{ET}CO_2$. A slight decrease in pH, ABE and SBC (Figures 1 and 2), and SBE was seen in series A at the end of the experiment. The pO_2, however, increased as estimated by pulse oxymetry and as measured in blood. In both series 70% FiO_2 caused an increase of pO_2 from 95–100 mmHg to 350 mmHg (Figure 3). In both control groups O_2 parameters tO_2, sO_2, p50, RHb and O_2Hb, as well as the lactate and HCO_3- concentrations remained unchanged.

In superficially ventilated animals (series A) the CO_2-pneumoperitoneum (group two) caused a pronounced and progressively increasing carboxaemia, as evidenced by the elevated pCO_2 (Figure 1, $P < 0.001$), tCO_2 (not shown, $P < 0.05$) and $P_{ET}CO_2$ (not shown, $P < 0.01$) in comparison with the control group. This CO_2 accumulation caused acidemia, which was initially a respiratory acidosis and subsequently a metabolic acidosis as shown by the progressively decreasing pH ($P < 0.001$) and the increased concentrations of lactate ($P < 0.05$) and HCO_3- after 90 min ($P < 0.001$) (Figure 2). The carboxaemia also affected the acid base balance as manifested by a progressively increasing deficiency of ABE ($P < 0.001$), SBE (not shown, $P < 0.001$) and SBC ($P < 0.001$). Simultaneously sO_2 ($P < 0.01$) and the O_2Hb ($P < 0.05$), concentration decreased, whereas the p50 ($P < 0.001$) and the concentration of RHb ($P < 0.001$), increased (Figure 2). The pO_2 ($P < 0.001$) and tO_2 (not shown, $P < 0.01$) decreased at the end of the experiment.

In superficially ventilated animals (series A) adding 6% of O_2 to the CO_2-pneumoperitoneum (group three) dramatically changed (Figures 1 and 2) the effects of pure CO_2 (group two). In comparison with pure CO_2 the carboxaemia (pCO_2) and acidosis (pH) were not only less pronounced ($P < 0.001$ for both values), but after 60 min a plateau was observed, whereas with pure CO_2 both effects increased progressively at least until 150–180 min. Metabolic acidosis was much less pronounced, and the lactate concentrations showed a small increase only, at the end of the experiment. In comparison with the pure CO_2-pneumoperitoneum group, the p50 (group two versus group three; $P < 0.001$) increased less whereas the values of ABE (group two versus group three; $P < 0.01$), SBC (group two versus group three; $P < 0.01$) and SBE (not shown, group two versus group three; $P < 0.01$), sO_2 (group two versus group three; $P < 0.01$) and O_2Hb (group two versus group three; $P < 0.05$), tO_2 (not shown, group two versus group three; $P < 0.01$) remained within background levels.

In adequately ventilated animals (series B) the effects of pure CO_2-pneumoperitoneum (group two) were similar but much less pronounced than in superficially ventilated animals (series A versus B: all values $P < 0.001$), i.e. slight carboxaemia with moderately increased arterial pCO_2 (group one versus

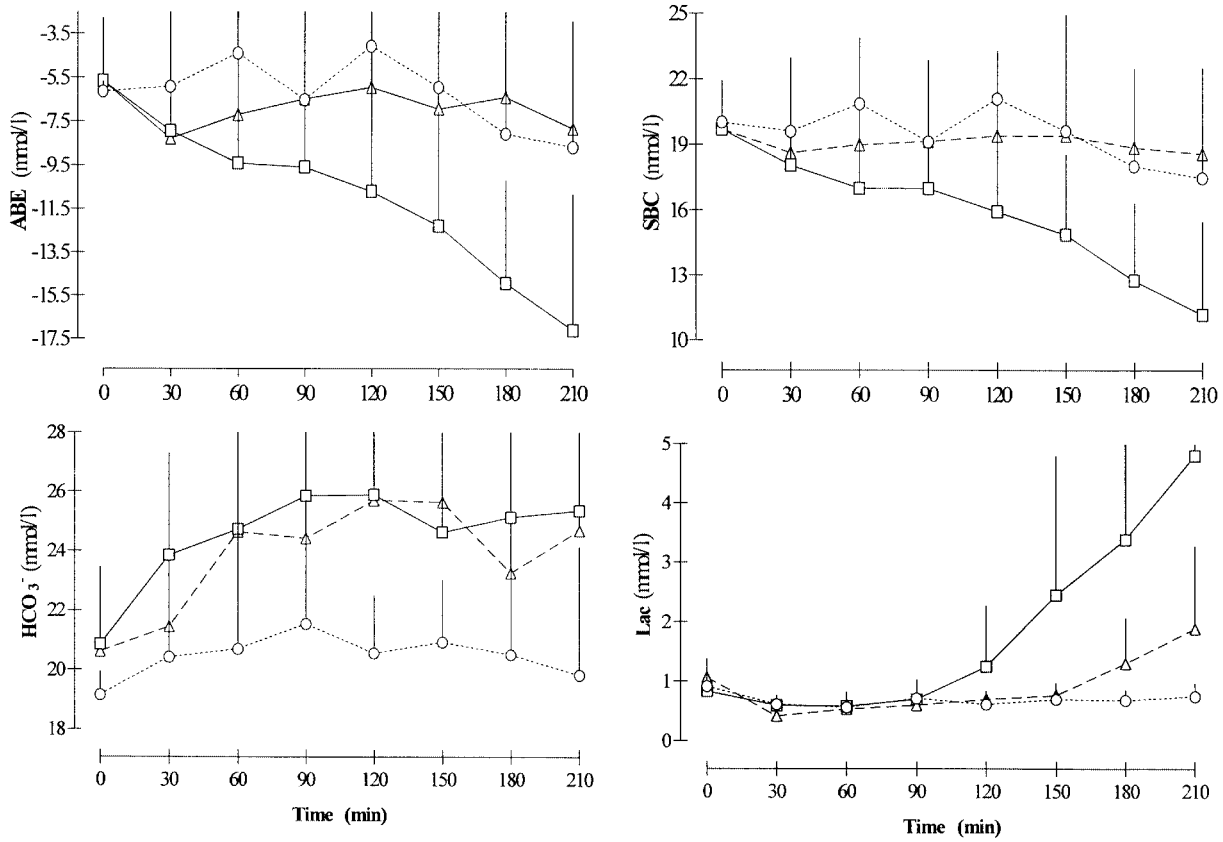

Figure 2. Arterial acid base (ABE, SBC and HCO_3-) values and metabolite (lactate) concentrations in rabbits. Series A; without pneumoperitoneum (group one —◇—), during pneumoperitoneum with 100% CO_2 (group two —□—) and 6% O_2 + 94% CO_2 (group three —△—). X: time, min and Y: means ± SD are given.

two; $P < 0.001$), tCO_2 (not shown, group one versus two; $P < 0.001$) and $P_{ET}CO_2$ (not shown, group one versus two; $P < 0.001$) and a slight respiratory acidosis (pH, group one versus two; $P < 0.001$) (Figure 1) without metabolic acidosis. In series B the effects of adding 6% of O_2 were similar to those in series A, i.e. less carboxaemia, almost no acidosis, and no changes for acid base and O_2 parameters.

Discussion

CO_2 used for the pneumoperitoneum during laparoscopy is absorbed in humans (Shuto *et al.*, 1995; Berg *et al.*, 1997) and in large (Leighton *et al.*, 1993; Liem *et al.*, 1996) and small animals (Kuntz *et al.*, 2000). The resulting increase of arterial pCO_2 and decrease of pH can be stabilized within 15–40 min by adequate ventilation (Kotzampassi *et al.*, 1993; Leighton *et al.*, 1993). Inadequate ventilation can lead to respiratory and metabolic acidosis and changes in acid base balance (Shuto *et al.*, 1995; Liem *et al.*, 1996; Berg *et al.*, 1997; Gebhardt *et al.*, 1997; Taura *et al.*, 1998). These effects are known to increase with pneumoperitoneum pressure, because of increased absorption and impaired CO_2 excretion and venous return (Shuto *et al.*, 1995; Liem *et al.*, 1996; Bazin *et al.*, 1997).

These observations are confirmed in our experiments—in animals with superficial ventilation and higher insufflation pressure (10 mmHg)—changes in both arterial pCO_2 and pH are more pronounced without reaching equilibrium within the first hours. In animals with adequate ventilation and lower insufflation pressure (6 mmHg) a slight increase of arterial pCO_2 and a slight decrease of pH, which stabilizes after 15–40 min, are seen. These results are also consistent with the recently reported arterial pCO_2 and pH changes in rabbits (Portilla *et al.*, 1998).

The reported data on acid base balance and O_2 values in blood during endoscopic surgery are not consistent. The HCO_3-concentration in arterial blood is reported to increase (Liem *et al.*, 1996), to decrease (Shuto *et al.*, 1995; Gandara *et al.*, 1997) or to remain constant (Leighton *et al.*, 1993; Wright *et al.*, 1995). The concentration of SBC has been reported to remain unchanged (Leighton *et al.*, 1993). The hydrogen ion concentration (H^+) increases (Wright *et al.*, 1995; Taura *et al.*, 1998) whereas the base excess (BE) decreases (Shuto *et al.*, 1995; Fernandez-Cruz *et al.*, 1998; Taura *et al.*, 1998) or remains stable (Horzic *et al.*, 1998). The arterial blood concentrations of lactate can increase (Berg *et al.*, 1997; Taura *et al.*, 1998) or decrease (Knolmayer *et al.*, 1998). The pO_2 is proportional to the FiO_2, e.g. a FiO_2 increase from 20–100% causes a pO_2 increase from 95–100 to 500 mmHg respectively. During endoscopic surgery with adequate ventilation pO_2 and sO_2 do not change (Leighton *et al.*, 1993). With higher intraperitoneal pressures, however, a slight decrease of pO_2 and sO_2 in arterial and mixed venous blood was described i.e. with pressures >12 mmHg in humans (Wright *et al.*, 1995;

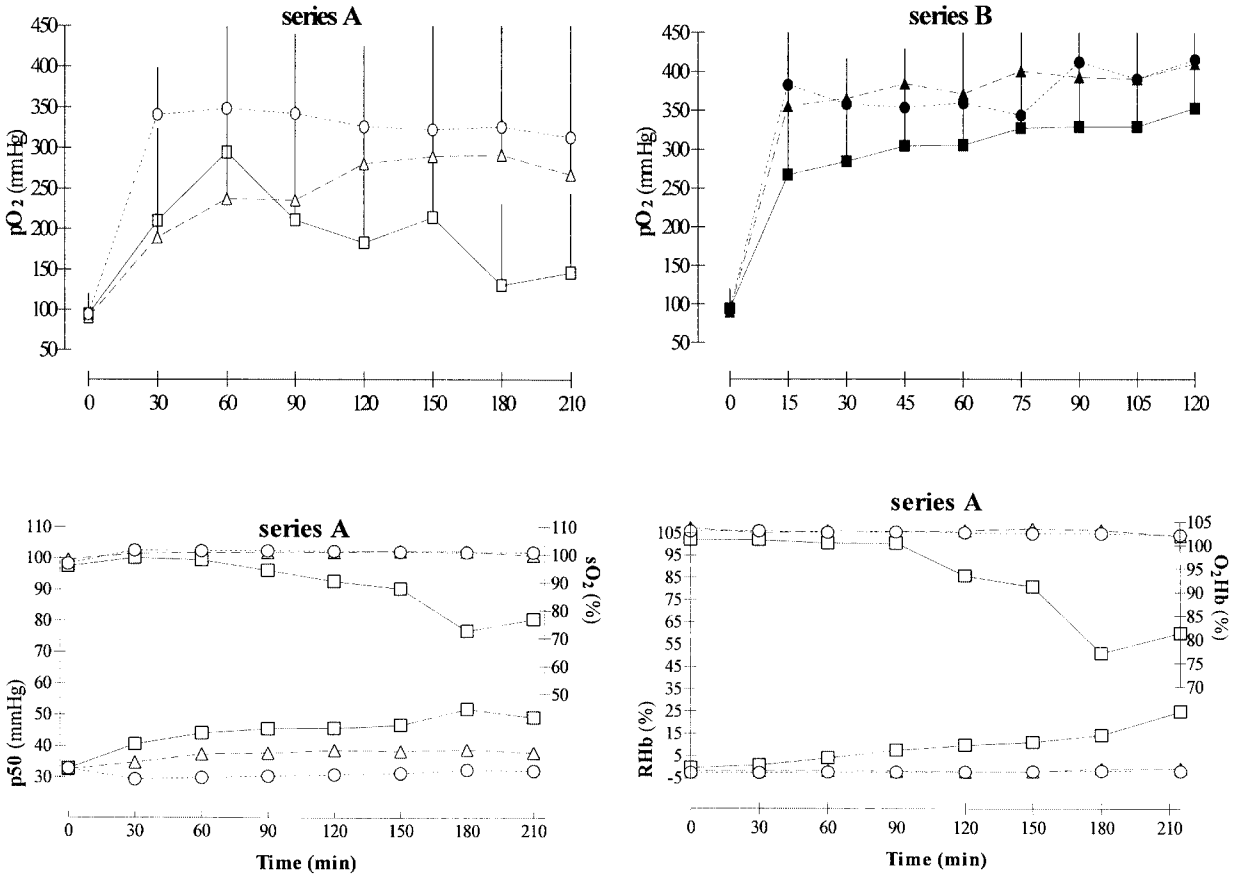

Figure 3. Arterial blood partial pressures of O_2 (pO_2), oximetry (sO_2, O_2Hb and RHb) and O_2 status (p50 or O_2 tension at half saturation assessing the haemoglobin O_2 affinity) parameters in rabbits without pneumoperitoneum (group one —◇— and —◆— in series A and B respectively), during pneumoperitoneum with 100% CO_2 (group two —□— and —■— in series A and B respectively) and 6% O_2 + 94% CO_2 (group three —△— and —▲— in series A and B respectively). X: time, min and Y: means ± SD are given (pO_2).

Berg *et al.*, 1997; Gebhardt *et al.*, 1997), >14 mmHg in dogs (Kotzampassi *et al.*,1993), and >10 mmHg in pigs (Liem *et al.*, 1996).

Our data give a comprehensive picture of changes caused by CO_2 absorption and confirm previous results (Mynbaev *et al.*, 2002). The key event is the progressive accumulation of CO_2, causing increases in carbonic acids and a base deficit. This leads initially to respiratory and later to metabolic acidosis. Excess of acids, base deficits and a lower pH reduce haemoglobin O_2 affinity, as evidenced by the increased O_2 tension at half saturation (p50), the increased concentration of reduced haemoglobins (RHb) and the decreased pO_2, sO_2 and O_2Hb, known as the Bohr effect (Siggaard-Andersen *et al.*, 1990). This results in tissue ischaemia and increased lactate concentrations (Berg *et al.*, 1997; Taura *et al.*, 1998).

The addition of 6% of O_2 to the CO_2 pneumoperitoneum has important and unexpected effects. The increase of pCO_2 and decrease of pH is much less than with pure CO_2-pneumoperitoneum and a plateau is reached after some 60 min, whereas with pure CO_2 the increase continues up to the end of the experiment. All subsequent effects such as an increase in HCO_3- and a decrease in ABE, SBE, SBC, pO_2, sO_2, O_2Hb and haemoglobin O_2 affinity are less pronounced or non-existent. The increase in lactate concentrations occurs much later and is less pronounced.

The progressive rise of pCO_2 and decline of pH during CO_2-pneumoperitoneum could be interpreted as an accumulation of resorbed CO_2. This hypothesis, however, does not explain the dramatic effect of adding 6% O_2 to the CO_2-pneumoperitoneum, since this only changes the CO_2 concentration from 100 to 94%. We therefore suggest another mechanism for the progressive rising CO_2 and declining pH during CO_2-pneumoperitoneum: namely that these effects do not accumulate, but reflect a progressively increasing absorption of CO_2 secondary to mesothelial damage by hypoxia. The addition of small amounts of O_2 to the CO_2 pneumoperitoneum prevents mesothelial damage. Hence, pCO_2 and pH changes occur for some 30 min only, i.e. the time to reach an equilibrium between absorption and evacuation by ventilation. This hypothesis of CO_2-pneumoperitoneum induced mesothelial damage through hypoxia and its prevention by adding small amounts of O_2 has been described previously (Yesildaglar *et al.*, 1999, 2000; Molinas and Koninckx, 2000; Molinas *et al.*, 2001) based on data in rabbits (Molinas and Koninckx, 2000; Yesildaglar *et al.*, 2000) and mice (Yesildaglar *et al.*, 1999; Molinas *et al.*, 2001) showing that adhesion formation increases with the duration of CO_2- or helium-pneumoperitoneum and with insufflation pressure, and decreases with the addition of small amounts of O_2 (Yesildaglar *et al.*, 1999, 2000; Molinas and Koninckx, 2000; Molinas *et al.*, 2001). To explain why the

addition of 6% of O_2 to the CO_2-pneumoperitoneum does not change HCO_3- and tCO_2 whereas pCO_2, pH, ABE, SBE, SBC, pO_2, sO_2, O_2Hb, RHb p50 and lactate are affected is more difficult. Factors that should be taken into consideration include: that CO_2-pneumoperitoneum finally leads to metabolic hypoxia (Mynbaev *et al.*, 2002) through the Bohr effect and that CO_2-pneumoperitoneum not only induces mesothelial hypoxia but also causes some hypoxia in the organs of the abdominal cavity. In order to understand the effect of the addition of O_2 to CO_2 on blood gases, acid base and O_2 homeostasis, it could also be compared with the treatment of hypoxia with O_2. Acute asphyxia increases the arterial pCO_2 and lactate concentration. Exercise hypoxia causes lactacidemia with increases in arterial lactate and decreases in pH, pCO_2, HCO_3-, base excess, sO_2 and haemoglobin O_2 affinity (Wasserman, 1986; Yoshida *et al.*, 1989). Treatment with O_2 normalizes the acid base balance and blood gases with a decrease of acid excess, compensation of base deficit, increases in saturation and in haemoglobin O_2 affinity (Adams and Welch, 1980; Yoshida *et al.*, 1989). Similarly, the addition of 6% of O_2 to the CO_2 could prevent the mesothelial hypoxemia and the metabolic changes in the peritoneum and in the organs of the abdominal cavity with subsequent stabilization of the acid base and blood gases homeostasis.

The concept that the addition of small amounts of O_2 to the CO_2 prevents hypoxic damage to the mesothelium and splanchnic organs, could explain the clinical observation that the absorption of CO_2 is more important during retroperitoneal surgery in humans. The effects of pneumoperitoneum observed in non-animal studies obviously cannot be extrapolated to human surgery. Indeed, in the human, increased ventilation is performed during surgery in order to keep pCO_2 within acceptable limits. In our experiments, we intentionally have chosen not to increase ventilation in order to show the effects clearly. Moreover, a model with superficial ventilation was used to enhance changes in order to better understand the underlying mechanism. This could be important in the human where similar hypoventilation experiments obviously cannot be performed, for ethical reasons.

In conclusion, the addition of 6% of O_2 to CO_2 used for the pneumoperitoneum dramatically affects the known increase in arterial pCO_2 and decrease in pH, with, in addition, a prevention of the subsequent metabolic changes. The prevention of local hypoxia in the peritoneum and in the organs of the abdominal cavity is suggested as a mechanism. If these preliminary data are confirmed in the human, the addition of a few percent of O_2 to CO_2 could become important during endoscopic surgery of longer duration, especially in patients with limited cardio-respiratory adaptation and steep Trendelenburg.

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