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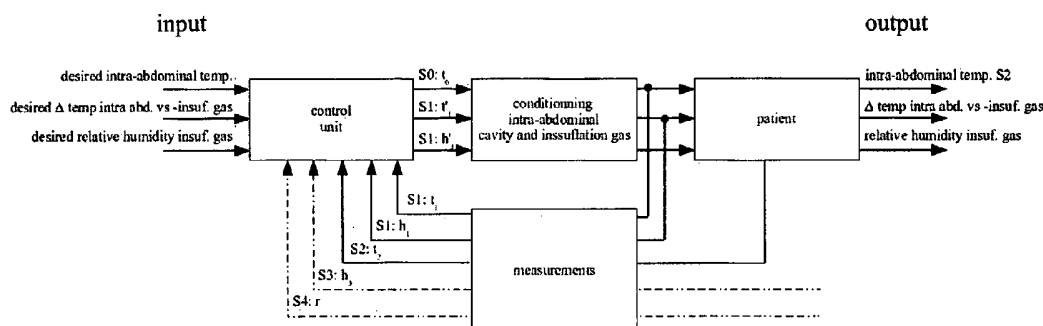
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(54) Title: ADHESION PREVENTION AND AN INTRA-LUMINAL COOLING SYSTEM THEREFOR



(57) Abstract: By present invention it has been found that hypothermia decreases adhesion formation more specifically pneumoperitoneum-enhanced adhesion formation. A cooling system has been designed to reduce the peritoneal cavity temperature during surgery, while maintaining at all times a 100% relative humidity in order to prevent desiccation, and a regulatory unit designed to condition the insufflated gas to achieve this while minimalising the necessary cooling. This is a new method for more effectively preventing adhesion though cooling while preventing desiccation. In mice it was demonstrated that factors such as environmental temperature, anaesthesia, ventilation and pneumoperitoneum can be used to influence body temperature in order to prevent adhesion formation.

WO 2005/117779 A1

**ADHESION PREVENTION AND AN
INTRA-LUMINAL COOLING SYSTEM
THEREFOR**

5 FIELD OF THE INVENTION

The present invention relates to adhesion formation prevention in general and to a cooling system and in particular to a system to reduce the temperature in the peritoneal cavity and to a regulatory unit permitting to obtain this cooling without dessication, and to a method for
10 preventing adhesion formation in particular.

BACKGROUND OF THE INVENTION

Postoperative adhesion formation is a major clinical problem because of their complications,
15 such as bowel obstruction (Ellis H Eur J Surg Supp 15-9, 1997), chronic pelvic pain (Duffy DM, DiZerega GS, J Reprod Med 41:19-26, 1996) and female infertility (Gomel V: Fertil Steril 40:607-611, 1983) and prolonged surgical time and postoperative complications (when additional surgical procedures are needed). The most common cause is prior surgery. The most frequent surgical procedures implicated in significant adhesion formation are
20 gynecologic, cardiovascular, and general abdominal surgery. This is true for traditional surgery, as well as laparoscopic surgery.

The pathophysiological events involved in adhesion formation are well known (Holmdahl L
25 et al, Eur J Surg Suppl 56-62, 1997 and DiZerega GS, Eur J Surg Suppl 10-16, 1997) and can

be summarized as follows: A peritoneal defect will cause exudation, fibrin deposition, followed by an inflammatory reaction, fibrinolysis and complete reepithelialisation within 3 to 8 days. This rapid healing is a consequence of the regeneration of the mesothelial layer from multiple foci in the lesion and not from the borders as is found during repair of another epithelium. The direct consequence of this is that the duration of reepithelialisation is independent of the denuded area in the peritoneum. If this rapid healing process fails by an overload of fibrin (e.g. through bleeding), by a decreased fibrinolysis (e.g. as a consequence of a more severe tissue trauma), resulting in a persistent fibrin matrix (Bittinger F, J Surg Res 82:28-33, 1999), or by the presence of a prolonged inflammatory reaction (e.g. by an infection or by suture material), this will lead to prolonged fibroblast proliferation, collagen deposition, angiogenesis and ultimately adhesion formation.

Exact data on the prevalence and severity of these consequences are not available since adhesions vary with the severity of surgery, and since systematic second look laparoscopies cannot be performed for obvious ethical reasons. Adhesions occur in over 50 % of patients following a laparotomy, whereas the risk of reintervention because of adhesions following a laparotomy was recently estimated at 35% within 10 years in a large survey in Scotland (Ellis H. et al, Lancet 353:1476-1480, 1999). Adhesion formation is a major problem following surgical procedures and is a frequent cause of postoperative pain and of infertility. Adhesions are the major cause of intestinal obstruction and it is estimated that following an intra-abdominal procedure, adhesions occur in some 50 to 80 percent of patients.

Thus, there is a need in the art for methods and compositions for inhibiting adhesion formation in patients..

Endoscopy also called minimal access surgery has become widely used over the last years because of clear-cut advantages of a decreased postoperative morbidity, less pain and a shorter hospitalisation. These procedures require by means of an insufflation system or an irrigation system a distension to permit visualisation. Endoscopic surgery uses a gas stream such as carbon dioxide gas (CO₂). Since anoxemia is a major cause and/or cofactor of adhesion formation, a gas mixture of CO₂ /O₂ in suitable proportions has now been used to reduce adhesion formation has been proposed (US6428500).

However pneumoperitoneum, and in particular CO₂ pneumoperitoneum, remains a co-factor in adhesion formation.

We now have evaluated in a laparoscopic mouse model the specific effect of cooling upon adhesion formation under CO₂ pneumoperitoneum and CO₂ /O₂.

First, the effect of body temperature upon basal and pneumoperitoneum-enhanced adhesion formation was evaluated in mice placed at room temperature (RT) or at 37°C. Secondly, the effect of using humidified air for ventilation upon body temperature was evaluated. Subsequently, the effect of body temperature (range: 32°C to 37°C) upon adhesion formation was evaluated in detail. Finally, in mice with a body temperature kept at 37°C, the pneumoperitoneum-enhanced adhesion formation by pure CO₂, together with the effects of adding 3% or 12% of oxygen, were confirmed.

It was surprisingly found that pneumoperitoneum-enhanced adhesion formation is much less at lower body temperatures.

A decrease in body temperature can be the consequence of anaesthesia and of desiccation when non-humidified gas is used either for ventilation or for pneumoperitoneum. We confirmed at an environmental temperature of 37 °C that the addition of 3% of oxygen to the pneumoperitoneum decreases adhesion formation and that 12% of oxygen causes more adhesions than 3%.

Moreover it was surprisingly found and clearly demonstrated that hypothermia reduces adhesion formation. A system for inducing and controlling hypothermia has been designed for prevention of adhesion prevention in mammalian, preferably human, surgery and preferably for endoscopic surgery.

DETAILED DESCRIPTION

Illustrative embodiment of the invention

During laparoscopy pneumoperitoneum is necessary to create a working space and CO₂ is generally used for safety reasons, i.e. a high solubility in water and a high exchange capacity in the lungs. CO₂ pneumoperitoneum is well known to cause systemic and local effects. Systemically, CO₂ pneumoperitoneum produces hypercarbia and acidosis (Junghans *et al.*, 1997; Liem *et al.*, 1996). Locally, CO₂ pneumoperitoneum decreases the pH (Volz *et al.*, 1996), alters microcirculation (Taskin *et al.*, 1998) and morphology of the mesothelial cells (Hazebroek *et al.*, 2002; Volz *et al.*, 1999; Suematsu *et al.*, 2001).

In addition, during CO₂ pneumoperitoneum body temperature can decrease, especially when cold and dry CO₂ gas at high flow rates is used (Bessell *et al.*, 1999). As can be

expected from thermodynamics, this cooling effect is caused less by the gas temperature but mainly by the energy necessary to evaporate body water in order to humidify the dry CO₂ (Bessell *et al.*, 1995). Indeed, cooling cannot be prevented with warm and dry gas (Bessell *et al.*, 1995; Hazebroek *et al.*, 2002), whereas cooling can be prevented to a large extent by cold and humidified gas (Hazebroek *et al.*, 2002). Cooling can be fully prevented using warm and humidified gas, as shown in rats (Hazebroek *et al.*, 2002), pigs (Bessell *et al.*, 1995; Bessell *et al.*, 1999; Mouton *et al.*, 1999) and humans (Puttick *et al.*, 1999). Effort in the art were the prevention of any cooling effect on the patient's body cavity and the place of surgery.

Pneumoperitoneum with dry and cold CO₂ alters the morphology of the mesothelium, i.e., destroys hexagonal pattern, reduces the microvilli (Hazebroek *et al.*, 2002) and bulges up the cells (Volz *et al.*, 1999; Suematsu *et al.*, 2001). These effects of dry and cold CO₂ are also observed in the pleural mesothelium after thoracoscopy (Mouton *et al.*, 1999). Whether this can be prevented by using warm and humidified gas is unclear, since both prevention (Mouton *et al.*, 1999) and no effect (Hazebroek *et al.*, 2002) were reported. Anyway, since the introduction of high flow insufflators for endoscopic surgery in the human (Koninckx and Vandermeersch, 1991), the CO₂ used became progressively warmed and humidified. The use of warm and humidified gas was claimed to reduce postoperative pain and duration of hospitalisation (Demco 2001) and to reduce intraperitoneal cytokine response (Puttick *et al.*, 1999) and tumour growth (Nduka *et al.*, 2002).

Over the last years CO₂ pneumoperitoneum became known as a cofactor in postoperative adhesion formation (Ordonez *et al.*, 1997; Molinas and Koninckx 2000; Molinas *et al.*, 2001). Several mechanisms seem to be involved. Firstly, mesothelial hypoxia triggering angiogenesis was suggested as a mechanism, since the effect increased with duration of pneumoperitoneum and with insufflation pressure, since similar effects were observed with helium pneumoperitoneum, since the addition of 2-4% of oxygen to both CO₂ and helium

pneumoperitoneum decreased adhesion formation (Molinas and Koninckx 2000; Molinas *et al.*, 2001), since this effect was absent in mice deficient for hypoxia inducible factor (HIF) (Molinas *et al.*, 2003b), plasminogen activator 1 (PAI-1) (Molinas *et al.*, 2003a), vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) (Molinas *et al.*, 2003c).

5 Secondly, a role for reactive oxygen species (ROS) in the adhesion formation has been suggested (Binda *et al.*, 2003) since ROS activity increases during both laparotomy and laparoscopy, since they are produced during the ischemia/reperfusion process and since the administration of ROS scavengers decreases adhesion formation in several animal models. Thirdly, other mechanisms could be involved such as cooling and dessication.

10 During pneumoperitoneum desiccation and cooling are intimately linked. Since the exact roles of desiccation and cooling upon peritoneal damage, and upon adhesion formation has not yet been studied in detail, we planned to evaluate in our laparoscopic mouse model the specific effect of cooling during CO₂ pneumoperitoneum upon adhesion formation.

15 Definitions

A pneumoperitoneum is in the meaning for a gas introduced in the abdomen of a patient to achieve exposure during laparoscopy and laparoscopic surgery. A pneumoperitoneum during lapararoscopy and laparoscopic surgery can be achieved by insufflators and is in the meaning
20 of a means to inject a gas, for instance carbon dioxide into the peritoneum to achieve exposure during lapaoscopy and laporoscopic surgery for treatment of a certain disorder. Endoscopic insufflation system is in the meaning of an endoscope comprising an insufflator.

Hypothermia is in the meaning of a body temperature or regional body temperature
25 significantly below the normal body temperature in humans being 37°C(98.6°F). A moderate

body temperature, which is obtainable by surface cooling, is considered to be 23 – 32 °C and a profound hypothermia is considered to be a body temperature or a regional body temperature of 12 – 20°C.

- 5 A patient in this application is in the meaning of an animal, preferably a warm blooded animal, more preferably a mammal and most preferably a human that has been, will be or is subjected to a surgery treatment.

Results

10

In the first experiment (Figure 1), mice and equipment were kept either at an environmental RT or at 37°C. Mice were exposed to 10 min (T_{20} to T_{30}) or 60 min (T_{20} to T_{80}) of pneumoperitoneum for basal and pneumoperitoneum-enhanced adhesion formation. During anaesthesia and ventilation only (T_0 to T_{20}), body temperature decreased from some 15 36.5°C to 31°C and from 37.5°C to 35°C at RT and 37°C, respectively. At RT, body temperature further decreased to 28.5°C and to 26.5°C at T_{80} in mice with 10 min and with 60 min of pneumoperitoneum, respectively. At 37°C, body temperature remained constant up to T_{80} at some 34.5°C and 35.5°C for 10 min and 60 min of pneumoperitoneum, respectively. Overall, body temperatures were always lower after 60 min of pneumoperitoneum than after 20 10 min i.e. both at RT ($p<0.0001$) and at 37°C ($p=NS$); body temperatures also were always lower at RT than at 37°C i.e. after both 10 min ($p<0.0001$) and 60 min ($p<0.0001$) of pneumoperitoneum (Two-way ANOVA).

At RT, adhesion formation increased with the duration of pneumoperitoneum (10 min vs. 60 min: proportion: $p<0.05$), as demonstrated before. At 37°C, this effect of duration of 25 pneumoperitoneum was more pronounced (10 min vs. 60 min: proportion: $p=0.01$, total: $p=0.04$, extent: $p=0.02$, type: $p=0.03$). In addition, at 37°C adhesion formation was higher

than at RT, clearly for pneumoperitoneum-enhanced adhesions (proportions: $p=0.04$, total: $p<0.05$, extent: $p=0.03$) and slightly for basal adhesions ($p=NS$) (Figure 1, Table I, Mann Whitney test).

In the second experiment, body temperatures were some 1°C higher when humidified air was used for ventilation ($p=0.003$, Two-way ANOVA), being 38.1 ± 0.1 (T_0), 36.4 ± 0.1 (T_{10}), 35.9 ± 0.3 (T_{20}), 36.2 ± 0.5 (T_{30}), 36.5 ± 0.6 (T_{40}), 36.5 ± 0.6 (T_{50}), 36.8 ± 0.5 (T_{60}), 37.0 ± 0.5 (T_{70}) and 37.1 ± 0.5 (T_{80}) $^{\circ}\text{C}$ for humidified ventilation and 37.8 ± 0.4 (T_0), 36.1 ± 0.1 (T_{10}), 35.0 ± 0.4 (T_{20}), 35.3 ± 0.5 (T_{30}), 35.4 ± 0.5 (T_{40}), 35.8 ± 0.7 (T_{50}), 35.7 ± 0.6 (T_{60}), 35.6 ± 0.5 (T_{70}) and 36.1 ± 0.5 (T_{80}) for non-humidified ventilation.

In the third experiment (Figure 2), during anaesthesia and ventilation only (T_0 to T_{20}), body temperature decreased from 38°C to 35.5°C for group I and II and from 36.5°C to 31°C for group III. Afterwards, body temperature remained constant till T_{80} at some 37°C for group I, 36°C for group II and 32.5°C for group III (group I vs. III : $p<0.0001$, II vs. III: $p<0.0001$ and I vs. II : $p=0.02$). Body temperatures of groups IV, V and VI were similar to group I ($p=NS$, data not shown, Two-way ANOVA).

Pneumoperitoneum-enhanced adhesion formation decreased with body temperature (Pearson correlation: $p=0.0171$ for proportion; Figure 2, Table II). Compared with group I, pneumoperitoneum-enhanced adhesions were lower in group III (proportion: $p=0.04$; Mann Whitney test). Differences between the other groups failed to reach statistical significance.

As demonstrated previously (experiment I), we reconfirmed that in a 37°C chamber, adhesion formation increased when pneumoperitoneum is prolonged from 10 to 60 min (group VI vs. I: proportion: $p=0.04$, total: $p=0.02$, extent: $p=0.04$, type: $p=NS$, tenacity: $p=0.04$). In comparison with pure CO_2 (group I), the addition of 3% oxygen to the pneumoperitoneum (group IV) decreased adhesion formation (proportion: $p=0.03$, total: $p=0.04$, extent: $p<0.05$, type: $p=NS$, tenacity: $p=NS$). In comparison with the addition of 3%

of oxygen to the pneumoperitoneum (group IV), the addition of 12% of oxygen (group V) increased adhesions, although it failed to reach statistical significance (Figure 3, Table II).

In Figure 4, the data of experiments I and III are combined in order to show graphically the relationship between body temperature and pneumoperitoneum-enhanced adhesion formation.

5 Taken all data together, pneumoperitoneum-enhanced adhesion formation strongly decreased with lower body temperatures (Linear regression and Pearson correlation: $p=0.0036$ for proportion; $p=0.0251$ for total).

This study confirmed and extended previous data concerning of the effects of anaesthesia,
10 ventilation and pneumoperitoneum upon body temperature.

We confirmed that anaesthesia decreases mice body temperature, as demonstrated previously in rats (Torbaty *et al.*, 2000), mice (Gardner *et al.*, 1995) and humans (Buhre and Rossaint 2003). As expected, this cooling effect is influenced by the environmental temperature, being more pronounced at RT and less at 37°C. These observations are
15 consistent with the reported effect of operating room temperature in humans. Indeed, patients remain normothermic after anaesthesia when they are kept in a warmer operating room, whereas they become hypothermic when placed in an operating theatre with colder temperature (Morris and Wilkey 1970; Morris 1971a; Morris 1971b). This pure anaesthetic side effect is caused by cutaneous vasodilatation, which abolishes heat conservation.
20 Consequently, anaesthetised subjects become poikilothermic and their body temperature varies with environmental temperatures (Morris 1971b).

This study demonstrated in mice that non-humidified ventilation can decrease body temperature confirming previous data in humans (Fonkalsrud *et al.*, 1980; Bissonnette and
25 Sessler 1989; Dery 1973). Since unsaturated air will absorb water by evaporation from a wet

surface (Williams *et al.*, 1996), water loss from the respiratory ways is the most plausible explanation.

We previously demonstrated and confirmed in these experiments that desiccation caused by the gas used for the pneumoperitoneum causes cooling. Therefore non-humidified gas at higher flow rates causes important cooling since desiccation is important. For this reason, we took great care to prevent desiccation as much as possible by avoiding any flow through the abdomen (experiment I) and by humidifying the gas (experiment II and III). It is difficult to rule out completely at least some desiccation by the pneumoperitoneum since gas tight seals of the trocar insertions are extremely difficult to obtain and since any humidification less than 100% will cause some desiccation. This might explain that 60 min of pneumoperitoneum causes slightly more cooling than 10 min even if we tried to prevent desiccation as much as possible. These data obviously do not yet permit to rule out other simultaneous effects such as vascular compression and reduced circulation.

The relationship between desiccation and cooling is complex. First, desiccation causes cooling. Secondly, desiccation is more important at higher gas temperature since absolute humidity increases with temperature e.g. relative humidity of 100% corresponds to 25 mg of water/litre of gas at 25°C and to 44 mg of water/litre of gas at 37°C. This might explain that the effect upon adhesion formation can be variable if not both desiccation and cooling is strictly controlled. Therefore experiments evaluating the effect of desiccation might underestimate the effect since desiccation decreases temperature which itself reduces desiccation.

By present invention we clearly demonstrated the finding that hypothermia reduces adhesion formations. Not only pneumoperitoneum-enhanced adhesions increase with the

body temperature, but also the differences between basal and pneumoperitoneum-enhanced adhesion formation increases with body temperature.

Present invention demonstrates for the first time that hypothermia directly protect tissues
5 and cells from the pneumoperitoneum adhesion enhancing effect..

One possible reason might be that oxygen consumption by cells decreases with temperature. Hypothermia decreases the global cerebral metabolic rate during ischemia, slowing the breakdown of glucose, phosphocreatine and ATP and the formation of lactate and
10 inorganic phosphate (Erecinska *et al.*, 2003).

Another reason for the effect of hypothermia may be its effect on the ischemia-reperfusion process, pneumoperitoneum-enhanced adhesion formation can be considered as an ischemia-reperfusion process. Hypothermia reduces the production of ROS during reperfusion in brain
15 (Zhao *et al.*, 1996), forebrain (Horiguchi *et al.*, 2003), heart (Prasad *et al.*, 1992), gut (Attuwaybi *et al.*, 2003), endothelium (Zar and Lancaster, Jr. 2000) and muscle (Yoshioka *et al.*, 1992). Hypothermia improves recovery of energetic parameters during reperfusion (Erecinska *et al.*, 2003). Hypothermia also suppresses the inflammatory response after hepatic ischemia-reperfusion, decreasing the infiltration of polymorphonuclears (Patel *et al.*, 2000),
20 and the production of tumour necrosis factor-alpha, interleukin-1 beta and macrophage inflammatory protein-2 also decreases (Patel *et al.*, 2000; Kato *et al.*, 2002).

In the experiments of present application we also confirmed and extended to 37°C our previous observations at RT which showed that the addition of 3% of oxygen to the
25 pneumoperitoneum decreased pneumoperitoneum-enhanced adhesion formation, and that the

addition of 12% of oxygen in comparison with 3% of oxygen increases adhesion formation to a similar level as with pure CO₂.

5 Examples

The example which follows explains the invention:

Animals

The study was performed in 86 female, Naval Medical Research Institute (NMRI), 9 to 10 weeks old mice weighing 30-40 g. The animals were kept under standard laboratory conditions (temperature 20°-22°C, relative humidity 50-60%, 14 hours light and 10 hours dark) at the animals' facilities of the Katholieke Universiteit Leuven. They were fed with a standard laboratory diet (Muracon.G, Carsil Quality, Turnhout, Belgium) with free access to food and water at anytime. The study was approved by the Institutional Review Animal Care Committee.

Anaesthesia and ventilation

Animals were anaesthetised with intraperitoneal (i.p.) pentobarbital (Nembutal, Sanofi Sante Animale, Brussels, Belgium) with a dose of 0.08 mg/g. This time was considered as time 0 (T₀). Animal preparation started 10 min after anaesthesia (T₁₀). The abdomen was shaved and the animal was secured to the table in supine position. Endotracheal intubation was performed as described (Molinas *et al.*, 2001; Molinas *et al.*, 2003a; Molinas *et al.*, 2003b; Molinas *et al.*, 2003c; Elkelani *et al.*, 2002). Briefly, a ventilation cannula (blunt-edge 20-gauge needle; BD Microlance 3, Becton Dickinson, Fraga, Spain) was introduced in the trachea by transillumination of the vocal cords. The catheter was connected to a mechanical

ventilator (Mouse Ventilator MiniVent, Type 845, Hugo Sachs Elektronik-Harvard Apparatus GmbH, March-Hugstetten, Germany) and the animal was ventilated with non-humidified or humidified room air (according to the experiment) with a tidal volume of 250 μ L at 160 strokes/min until the end of the experiment (T_{80}).

5

Laparoscopic surgery

A midline incision was performed caudal to the xyphoides appendix and a 2-mm endoscope with a 3.3-mm external sheath for insufflation (Karl Storz, Tuttlingen, Germany) was introduced into the abdominal cavity. The endoscope, connected to a video camera and light source (Karl Storz, Tuttlingen, Germany), was secured in a holder and the incision was closed gas tight around the endoscope with 5/0 polypropylene suture (Prolene, Ethicon, Johnson and Johnson Intl, Brussels, Belgium) in order to avoid leakage (Molinas *et al.*, 2001; Molinas *et al.*, 2003a; Molinas *et al.*, 2003b; Molinas *et al.*, 2003c; Elkelani *et al.*, 2002).

15 The pneumoperitoneum was created after 20 min of injecting the anaesthesia (T_{20}) using the Thermoflator Plus (Karl Storz, Tuttlingen, Germany), which permits to add a variable concentration of O_2 to the CO_2 . Insufflation gas, humidification and temperature varied with the experimental design. For humidification the Storz Humidifier 204320 33 (Karl Storz, Tuttlingen, Germany) was used. Gas temperature was determined by the ambient temperature
20 i.e. either 23-25°C (RT) or 37°C. Indeed, previous experiments showed equilibration of the gas temperature before some 50 cm of tubing using 7-mm inner diameter tubing and a flow rate of 2.5 L/min. The Thermoflator Plus was preset with a flow rate of 2.5 liters/min and a pressure of 18 mm Hg. A water valve was used to dampen pressure changes and to ascertain a continuous insufflation pressure of 20 cm H_2O (\cong 15 mm Hg) since any excess of CO_2 freely
25 escapes from the water valve, whereas pressure is maintained accurately in the water valve.

Induction of intraperitoneal adhesions

After the establishment of the pneumoperitoneum (T₂₀), two 14-gauge catheters (Insyte-W, Vialon, Becton Dickinson, Madrid, Spain) were inserted under laparoscopic vision in both right and left flank for the working instruments. The uterus was grasped in the midline with a 1.5-mm grasper and standardized 10-mm x 1.6-mm lesions were performed in the antimesenteric border of both right and left uterine horns with monopolar coagulation using a homemade 1.6-mm ball probe (10 watts, standard coagulation mode, Autocon 350, Karl Storz, Tuttlingen, Germany). In addition, identical lesions were made in both right and left pelvic sidewalls.

In order to evaluate basal and pneumoperitoneum-enhanced adhesion formation, the pneumoperitoneum was maintained for the minimum time needed to perform the surgical lesions, standardized at 10 min (T₂₀ to T₃₀), or for 60 min (T₂₀ to T₈₀), respectively (Molinas *et al.*, 2001). The secondary ports were removed after finalizing the peritoneal lesions and the incisions were closed. All incisions were closed in a single layer with 5/0 polypropylene suture (Prolene, Ethicon, Johnson and Johnson Intl, Brussels, Belgium).

Scoring of adhesions

A surgeon who was blinded of the group being evaluated performed a xyphopubic midline incision and a bilateral subcostal incision to explore the whole abdominal cavity during laparotomy seven days after the induction of adhesions (Molinas *et al.*, 2001; Molinas *et al.*, 2003a; Molinas *et al.*, 2003b; Molinas *et al.*, 2003c; Elkelani *et al.*, 2002). After the evaluation of port sites and viscera, the pelvic fat tissue was carefully removed and adhesions were scored under microscopic vision using a qualitative and a quantitative scoring system. In the qualitative scoring system the following characteristics were assessed: *extent* (0: no

adhesions; 1: 1-25%; 2: 26-50%; 3: 51-75%; 4: 76-100% of the injured surface involved, respectively), *type* (0: no adhesions; 1: filmy; 2: dense; 3: capillaries present), *tenacity* (0: no adhesions; 1: easily fall apart; 2: require traction; 3: require sharp dissection) and *total* (extent + type + tenacity). In the quantitative scoring system (Holmdahl *et al.*, 1994), the proportion of the lesions covered by adhesions was measured using the following formula: adhesions (%) = (sum of the length of the individual attachments/length of the lesion) x 100. The results are presented as the average of the adhesions formed at the four individual sites (right and left visceral and parietal peritoneum), which were individually scored.

10 Environment and animal temperatures

To control temperature, animals and equipment, i.e. insufflator, humidifier, water valve, ventilator and tubing, were placed in a closed chamber maintained either at RT or at 37°C (heated air, WarmTouch, Patient Warming System, model 5700, Mallinckrodt Medical, Hazelwood, MO, USA). Temperature of the environment was measured with Testo 645 (Testo N.V./S.A., Lenzkirch, Germany), whereas temperature of the animal was measured in the rectum with the Hewlett Packard 78353A device (Hewlett Packard, Böblingen, Germany) and recorded every 10-20 min from T₀ to T₈₀.

Experimental design

20 In the first experiment (n=32), basal and pneumoperitoneum-enhanced adhesion formation, together with body temperature, were evaluated in mice placed either at RT or at 37°C. In this experiment non-humidified CO₂ was used for the pneumoperitoneum and special care was taken to have a gas tight seal around the trocar in order to avoid any flow through the peritoneum and thus minimize desiccation. Ventilation was performed with non-humidified air (4 groups, n=8 per group).

In the second experiment (n=6), the effect of ventilation with or without humidified air upon body temperature was evaluated in mice placed at 37°C during 60 min of humidified CO₂ pneumoperitoneum (2 groups, n=3 per group).

The third experiment (n=48) was designed to evaluate in detail the effect of body temperature (range: 32°C to 37°C) upon adhesion formation. To achieve a body temperature with minimal cooling, i.e. around 37°C, mice were placed at 37°C and ventilated with humidified air. To achieve a slightly lower body temperature, i.e. around 36°C, mice were placed at 37°C and ventilated with non-humidified air. To achieve a body temperature of some 32°C, mice were placed alternatively at RT (T₀-T₂₀, T₃₀-T₄₀, T₅₀-T₆₀ and T₇₀-T₈₀) and at 37°C (T₂₀-T₃₀, T₄₀-T₅₀ and T₆₀-T₇₀) and ventilated with humidified air. These settings were determined based on previous experiments. Pneumoperitoneum-enhanced adhesion formation was evaluated using pure and humidified CO₂ in mice at 37°C (group I), 36°C (group II) and 32°C (group III). Pneumoperitoneum-enhanced adhesion formation at 37°C was also evaluated using humidified CO₂ with 3% of oxygen (group IV) and 12% of oxygen (group V). Simultaneously, basal adhesion formation was evaluated using pure and humidified CO₂ (group VI). A flow of 23 ml/min through the pneumoperitoneum was used in all the groups (6 groups, n=8 per group).

Statistics

Statistical analyses were performed with GraphPad Prism version 4 for Windows 95 (GraphPad Software Inc., San Diego California USA.). Mann Whitney test was used to compare adhesion formation between individual groups. Intergroup differences in body temperature were evaluated with two-way ANOVA. Linear regression and Pearson correlation were used to analyse adhesions and body temperature data. All data are presented as the mean ± standard error of the mean (SE).

5

Table I: Effect of environment temperature upon adhesion formation in mice.

Env.	Pneumoperitoneum			Adhesion scores (mean \pm SE)		
	Oxygen	Duration	Extent	Type	Tenacity	Total
25°C	0%	10 min	0.6 \pm 0.1	0.6 \pm 0.1	0.7 \pm 0.1	1.9 \pm 0.4
	0%	60 min	1.0 \pm 0.1	1.0 \pm 0.2	0.9 \pm 0.1	2.9 \pm 0.4
37°C	0%	10 min	0.9 \pm 0.1	0.9 \pm 0.1	1.0 \pm 0.1	2.8 \pm 0.3
	0%	60 min	1.8 \pm 0.2 ^{a,b}	1.5 \pm 0.2 ^a	1.3 \pm 0.2	4.5 \pm 0.6 ^{a,b}

Adhesions were induced during laparoscopy at 20 cm H₂O insufflation pressure.

^a 10 vs. 60 min at RT or 37°C, $p < 0.05$, ^b RT vs. 37°C, 10 or 60 min $p < 0.05$, Mann Whitney

10 Test.

Table II: Effect of the body temperature, of the addition of oxygen to pneumoperitoneum and of the duration of pneumoperitoneum upon adhesion formation in mice.

Group	Body Temp ^b (mean \pm SE)	Pneumoperitoneum			Adhesion scores (mean \pm SE)		
		Oxygen	Duration	Extent	Type	Tenacity	Total
I	36.2 \pm 0.2°C	0 %	60 min	1.7 \pm 0.2	1.3 \pm 0.1	1.4 \pm 0.1	4.4 \pm 0.4
II	35.9 \pm 0.1°C	0 %	60 min	1.4 \pm 0.2	1.2 \pm 0.3	1.2 \pm 0.2	3.7 \pm 0.6
III	32.2 \pm 0.2°C	0 %	60 min	1.0 \pm 0.2	0.9 \pm 0.2	1.1 \pm 0.2	3.1 \pm 0.5

IV	$36.4 \pm 0.1^{\circ}\text{C}$	3 %	60 min	$1.1 \pm 0.2^{\text{a}}$	1.1 ± 0.2	1.1 ± 0.1	$3.2 \pm 0.4^{\text{a}}$
V	$36.7 \pm 0.1^{\circ}\text{C}$	12 %	60 min	1.5 ± 0.2	1.3 ± 0.2	1.4 ± 0.2	4.1 ± 0.5
VI	$36.4 \pm 0.1^{\circ}\text{C}$	0 %	10 min	$0.9 \pm 0.2^{\text{a}}$	0.7 ± 0.2	$0.8 \pm 0.2^{\text{a}}$	$2.4 \pm 0.6^{\text{a}}$

Adhesions were induced during laparoscopy at 20 cm H₂O insufflation pressure.

^a p vs. group I <0.05, Mann Whitney Test.

^b Body temperature during T₂₀-T₈₀ is indicated.

5

Summary of the invention

The present invention relates to adhesion prevention in general and to a system and a method, alone or integrated in an assembly with an endoscopic insufflation system for preventing adhesion formation in particular. Adhesion formation is a major problem following surgical procedures and is a frequent cause of postoperative pain and of infertility. Adhesions are the major cause of intestinal obstruction and it is estimated that following an intra-abdominal procedure, adhesions occur in some 50 to 80 percent of patients.

15 The mechanism of adhesion formation can be summarized as follows: a trauma of the peritoneal lining is rapidly followed by an inflammatory reaction; exudation of plasma, and deposition of a fibrin matrix. Subsequently the lesion is healed by the degradation of the fibrin deposition, and by proliferation of the mesenchymal lining of the peritoneum. If the repair process is not completed within a few days, fibroblast proliferation starts which ultimately will end in collagen deposition and adhesion formation. Key players in this process are in particular fibrin and fibrinolysis, macrophages and their secretion products such as growth hormones and cytokines, and obviously the epithelial repair process. From this repair process it results that adhesion formation is largely independent from the extent of the trauma.

Since by present invention it has been surprisingly found that an intra-abdominal hypothermia or an hypothermia at the side of surgery can effectively reduce post operative adhesion, since it dessication was demonstrated for the first time to enhance adhesion formation and given the
5 known relationship between dessication and cooling, it is the aim of the present invention to provide an intra-abdominal cooling means, preferably an endoscopic system comprising the intra-abdominal cooling unit together with a humidifier and a regulatory unit permitting to achieve the desired cooling without dessication for more effectively preventing adhesion formation.

10

Surprisingly, it was found that cooling the tissue surface in a body cavity decreases the post-operative adhesion formation between tissue surfaces in a body cavity. The invention relates in particular to the induction of hypothermia on said tissue surfaces in said body cavity with or without a compound for the manufacture of a medicament for preventing adhesion
15 formation. Since desiccation enhances adhesion formation whereas absolute humidity increases with temperature, it is mandatory that the insufflated gas is at all times higher than the intra-abdominal temperature in order to prevent an increase in temperature which necessarily causes a decrease in relative humidity and thus desiccation. The absolute humidity of the insufflated gas should after cooling to the intra-abdominal temperature exceed the
20 absolute humidity at that temperature and thus cause condensation ensuring at all times a 100% relative humidity intra abdominally, thus preventing desiccation, whereas the condensated water becomes a means to deliver adhesion preventing drugs.

Given the relationship between temperature, humidity, and desiccation, a regulatory unit has been designed to optimise the achievement of an intra-abdominal temperature decreasing
25 from 37°C to 32°C, together with a continuously 100% relative humidity, preferably with

some condensation. Indeed the amount of cooling required in cal/min, will increase with the temperature of the insufflated gas, with the absolute humidity of this gas, and with the flow rate of the insufflation. The regulatory unit minimalises the amount of cooling by conditioning the temperature and absolute humidity of the insufflated gas. This is achieved by maintaining at all times the absolute humidity of the insufflated gas at least 1-2 mg/liter above 100% relative humidity at the intra-abdominal temperature, thus causing some condensation upon entrance in the abdominal cavity. The temperature and absolute humidity of the insufflated gas will thus vary with the intra-abdominal temperature,

It is the aim of the present invention to provide a cooling system to reduce the peritoneal cavity temperature during surgery, and a method for more effectively preventing adhesion. The environmental temperature, anaesthesia, ventilation and pneumoperitoneum can be used to influence the body temperature and more particularly the temperature of the intra-abdominal surface in order to prevent adhesion formation.

An important observation is that hypothermia decreases pneumoperitoneum-enhanced adhesion formation.

This could be due to prevention from the toxic effects caused by hypoxia and the ischemia-reperfusion process. Other effects, i.e. reduction of the inflammatory response, an increase of intestinal peristaltic movements, cannot be excluded. Whether basal adhesions i.e. without a pneumoperitoneum, are also decreased by lower temperatures, is still uncertain since in our model the group of 'basal adhesions' still had 10 min of pneumoperitoneum. If substantiated in larger animals that the decrease in adhesion formation is caused by a reduction in mesothelial temperature, i.e. that a reduction in the peritoneal cavity temperature is sufficient

and that the body temperature can be maintained at 37°C, the implications for the prevention of the adhesion formation in mammalian, preferably human, surgery are obvious.

5 The present invention involves a cooling assembly which is characterised in that it comprises an intra-luminal cooling means designed to cool a patient's body cavity or body cavity surface to a condition of hypothermia or regional hypothermia and wherein said cooling assembly comprises a cooling means (b) which is mountable to a controlling means (a) designed to regulate the intra-abdominal cooling while maintaining continuously a 95 to
10 100% relative humidity in the body cavity of said patient and which is mountable to a cooling conduit (c) designed to transport cooling fluid into the patient's body cavity or to a region of patient's body cavity. This assembly can be characterised in that the cooling conduit is designed to comprise a liquid fluid or to comprise a gas/liquid fluid. Moreover this assembly can be characterised in that the cooling conduit (c) is designed to sprinkle the
15 cooling fluid into the patient's body cavity or to a region of patient's body cavity.

In a particular embodiment the assembly is characterised in that the controlling means (a) is designed to regulate the intra-abdominal cooling while maintaining continuously a relative humidity of 96 to 100%, preferably a relative humidity of 99 to 100% and most preferably a
20 100% humidity in patient's body cavity.

In a particular embodiment the assembly of present invention is characterised in that it is integratable with or mountable to an insufflation assembly (N) designed to induce a pneumoperitoneum in a patient's body cavity. This insufflations assembly may comprise a

means for insufflation measurement and conditioning (e), an insufflation tubing (f), a humidifier (g), a humidifier (g) and an insufflator (i).

In another embodiment of present invention the assembly is characterised in that the
5 controlling means comprises at least one sensor to measure the temperature in the patient's body cavity, at least one sensor to measure the flow rate of the insufflation fluid, at least one sensor to measure the temperature of the insufflation fluid, at least one sensor to measure the humidity of the insufflation fluid and at least one actuator to condition the temperature and absolute humidity in the insufflation fluid. It may further comprise at least one sensor to
10 measure the flow rate in the cooling conduit.

In yet another embodiment of present invention the assembly is characterised in that the cooling conduit comprises a fluid guidance including an interior wall and an exterior wall, wherein said interior wall defines one boundary of said interior fluid guidance from a fluid
15 inlet in said exterior wall to a fluid outlet in said exterior wall.

The present invention may also involve an embodiment of an assembly that is characterised in that controlling means is designed to condition the temperature and absolute humidity of the insufflation fluid to an absolute humidity which is slightly higher than the relative
20 humidity at the intra-abdominal temperature. For instance the controlling means can be designed to condition the temperature and absolute humidity in the insufflation fluid to achieve an absolute humidity in said insufflation fluid which is 0.1 to 5 % higher than the relative humidity at the intra-abdominal temperature.

In a particular embodiment the assembly is characterised in that the controlling means is designed to adapt the cooling rate in the body cavity to maintain a continuously 97 – 100% relative humidity at the desired intra-abdominal temperature. To achieve this the controlling means can be designed to maintain a temperature in the insufflation fluid which is 1°C to 5 °C higher than the temperature in the body cavity or to maintain a temperature in the insufflation fluid which is 2°C to 4 °C higher than the temperature in the body cavity.

In a preferred embodiment the assembly of present invention is characterised in that its controlling means is designed to regulate the temperature, humidity and/or insufflation flow rate in the cooling conduit until a predestined temperature of the intra-abdominal surface between 32 – 23 °C has been reached or its controlling means can be designed to regulate the temperature, humidity and or insufflation flow rate in the cooling conduit until a predestined temperature of the intra-abdominal surface between 23 – 12 °C has been reached.

In yet another preferred embodiment the assembly can be characterised in that it cools the patient's body cavity or body cavity surface to a moderate hypothermia or that it cools the patient's body cavity or body cavity surface to a profound hypothermia

In a particular embodiment the assembly is characterised in that the fluid outlet of the cooling conduit is are near the proximal end of the trocar (L) of an endoscopic surgery device and in yet another embodiment that the cooling channel is extending coaxially within the trocar (L) of an endoscopic surgery device to the distal end thereof.

The an embodiment of present invention may also involve a method to prevent or decrease post-operative adhesion formation between tissue surfaces in a body cavity, wherein the

method prevents or decreases post-operative adhesion by cooling the tissue surfaces in said body cavity that is, has been or will be subjected to pneumoperitoneum and surgery, to a temperature and humidity that is effective to inhibit the formation of adhesions thereon. The method may comprise that the surfaces in a body cavity or part of the surface is cooled to a moderate hypothermia or to a profound hypothermia.

In a particular embodiment the method of present invention is further characterised in that the temperature of the insufflation fluid and absolute humidity of the insufflation fluid is conditioned to obtain an absolute humidity of the insufflation fluid that is higher than the relative humidity at the intra-abdominal temperature together for instance the temperature of the insufflation fluid and absolute humidity of the insufflation fluid can conditioned to obtain an absolute humidity of the insufflation fluid that is 0.1 to 5 % higher than the intra-abdominal relative humidity.

DRAWING DESCRIPTION

Brief description of the drawings

Figure 1

Effect of environment temperature upon body temperature (left side) and upon adhesion formation (right side) in mice. Basal and pneumoperitoneum (PP)-enhanced adhesions were induced during laparoscopy at 20 cm H₂O insufflation pressure and mice were kept either at RT or at 37°C.

Symbols: ○ 10 min PP, RT; ● 60 min PP, RT; □ 10 min PP, 37°C; ■ 60 min PP, 37°C

p<0.05: ^a 10 vs. 60 min at RT or at 37°C, ^b RT vs. 37°C at 10 or at 60 min (Two-way ANOVA for temperature and Mann Whitney test for adhesion formation)

Figure 2

Effect of body temperature (left side) upon adhesion formation (right side) in mice.

Pneumoperitoneum (PP)-enhanced adhesions were induced during laparoscopy at 20 cm H₂O insufflation pressure.

- 5 Symbols: □ group I, ▲ group II, ● group III. Mean ± SE of body temperature during T₂₀-T₈₀ is indicated on the adhesion graph.

p<0.05: ^a vs. group I, ^b vs. group II (Two-way ANOVA for temperature and Mann Whitney test for adhesion formation).

10 **Figure 3**

Effect at 37 °C of the duration of pneumoperitoneum and of adding oxygen to the pneumoperitoneum upon adhesion formation in mice. Basal (group VI) and pneumoperitoneum (PP)-enhanced adhesions (group I, IV and V) were induced during laparoscopy at 20 cm H₂O insufflation pressure with CO₂ containing 0% (group I and VI),

- 15 3% (group IV) or 12% of oxygen (group V). Mean ± SE of body temperature during T₂₀-T₈₀ is indicated. p<0.05: ^a vs group I, ^b vs group V (Mann Whitney test).

Figure 4

Relationship between body temperature and adhesion formation.

- 20 Individual values of the mean of body temperature between T₂₀ and T₈₀ with their respective proportion of adhesions are depicted for pneumoperitoneum-enhanced adhesion for experiment I and III. p=0.0036 (Pearson correlation).

Figure 5

Displays a cross-sectional side of a patient subjected to an insufflation for endoscopy. This insufflator can be integrated with an intra-abdominal cooling means designed to obtain an intra-abdominal temperature (K) below 37°C, preferably below 35 °C, ideally between 32 to 34°C, a humidification system to prevent completely dessication, and a regulatory unit

5 permitting to obtain simultaneously cooling, and absence of dessication.

J = patient, K = intra-abdominal cavity, L= trocar, N= is insufflator means and M is endoscope comprising camera and lighting

Figure 6 is a cross-sectional side view of an assembly for intra-abdominal cooling,

10 insufflation and humidification, wherein a = a control unit, b = an intra-abdominal cooling means, c= the intra-abdominal cooling conduit, d = an intra-abdominal temperature probe, e = a means for insufflation measurement and conditioning, f = a conditioned insufflation tubing, g = a humidifier, h = an insufflation tubing and i = an insufflator

The control and measurement signals are indicated by the following symbols: S0 = set point

15 intra-abdominal cooling t_0 ; S1 = the measurement of insufflation temperature t_1 , the measurement of insufflation relative humidity h_1 , the set point insufflation temperature t'_1 or the set point relative humidity h'_1 ; S2 = the measurement of the intra-abdominal temperature T_2 , S3 = the demanded relative humidity h_3 and S4 is the insufflation flow rate r .

20 **Figure 7** is a cross-sectional side view an intra-abdominal cooling means as which can be integrated into the assembly of figure 5 but demonstrating that alternatively the intra-abdominal cooling can be directed via the trocar of the endoscope.

b = an intra-abdominal cooling means, c= the site intra-abdominal cooling, d = an intra-abdominal temperature probe, e = a means for insufflation measurement and conditioning,

The control and measurement signals are indicated by the following symbols: S0 = set point intra-abdominal cooling t_0 ; S1 = the measurement of insufflation temperature t_1 , the measurement of insufflation relative humidity h_1 , the set point insufflation temperature t'_1 or the set point relative humidity h'_1 ; S2 = the measurement of the intra-abdominal temperature T_2 ,

Figure 8 is a feedback based control loop which can be used to regulate towards a desired intra abdominal temperature, the desired relative humidity of the insufflated gas and which can establish the necessary temperature difference between insufflated gas and intra abdominal temperature in order to get condensation of the insufflated gas in the abdominal cavity ensuring full humidification and preventing dessication. Optional input signals are shown as dashed lines, and comprise mainly the setpoint of the relative humidity of the humidifier and flow rate generated by the insufflator. This control mechanism is a concrete implementation of the aforementioned regulatory unit (**control unit figure 6 a**), but by no means the one and only workable solution.

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**ADHESION PREVENTION AND AN
INTRA-LUMINAL COOLING SYSTEM
THEREFOR**

5

CLAIMS

1) A cooling assembly characterised in that it comprises an intra-luminal cooling means designed to cool a patient's body cavity or body cavity surface to a condition of hypothermia or regional hypothermia and wherein said cooling assembly comprises a cooling means (b) which is mountable to a controlling means (a) designed to regulate the intra-abdominal cooling while maintaining continuously a 95 to 100% relative humidity in the body cavity of said patient and which is mountable to a cooling conduit (c) designed to transport cooling fluid into the patient's body cavity or to a region of patient's body cavity.

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2) The assembly of claim 1, characterised in that the cooling conduit is designed to comprise a liquid fluid.

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3) The assembly of claim 1, characterised in that the cooling conduit is designed to comprise a gas/liquid fluid.

4) The assembly of the claims 1 to 3, characterised in that the cooling conduit (c) is designed to sprinkle the cooling fluid into the patient's body cavity or to a region of patient's body cavity.

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5) The assembly of the claims 1 to 4, characterised in that the controlling means (a) is designed to regulate the intra-abdominal cooling while maintaining continuously a relative humidity of 96 to 100% in patient's body cavity.

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6) The assembly of the claims 1 to 4, characterised in that the controlling means (a) is designed to regulate the intra-abdominal cooling while maintaining continuously a 100% relative humidity in patient's body cavity.

10 7) The assembly of the claims 1 to 6, characterised in that it is integratable with or mountable to an insufflation assembly (N) designed to induce a pneumoperitoneum in a patient's body cavity.

15 8) The assembly of claim 7, wherein the insufflations assembly comprises a means for insufflation measurement and conditioning (e), an insufflation tubing (f), a humidifier (g), a humidifier (g) and an insufflator (i).

20 9) The assembly of the claims 1 to 8, characterised in that the controlling means comprises at least one sensor to measure the temperature in the patient's body cavity, at least one sensor to measure the flow rate of the insufflation fluid, at least one sensor to measure the temperature of the insufflation fluid, at least one sensor to measure the humidity of the insufflation fluid and at least one actuator to condition the temperature and absolute humidity in the insufflation fluid.

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10) The assembly of claim 9, characterised in that the intra-luminal cooling device further comprises at least one sensor to measure the flow rate in the cooling conduit.

11) The assembly of the claims 1 to 10, characterised in that the cooling conduit comprises a fluid guidance including an interior wall and an exterior wall, wherein said interior wall defines one boundary of said interior fluid guidance from a fluid inlet in said exterior wall to a fluid outlet in said exterior wall.

12) The assembly of the claims 1 to 11, characterised in that controlling means is designed to condition the temperature and absolute humidity of the insufflation fluid to an absolute humidity which is slightly higher than the relative humidity at the intra-abdominal temperature.

13) The assembly of claim 12, characterised in that controlling means is designed to condition the temperature and absolute humidity in the insufflation fluid to achieve an absolute humidity in said insufflation fluid which is 0.1 to 5 % higher than the relative humidity at the intra-abdominal temperature.

14) The assembly of the claims 1 to 13, characterised in that the controlling means is designed to adapt the cooling rate in the body cavity to maintain a continuously 97 – 100% relative humidity at the desired intra-abdominal temperature.

15) The assembly of the claims 1 to 14, characterised in that its controlling means is designed to maintain a temperature in the insufflation fluid which is 1°C to 5 °C higher than the temperature in the body cavity.

16) The assembly of the claims 1 to 14, characterised in that its controlling means is designed to maintain a temperature in the insufflation fluid which is 2°C to 4 °C higher than the temperature in the body cavity.

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17) The assembly of the claim 1 to 16, characterised in that its controlling means is designed to regulate the temperature, humidity and/or insufflation flow rate in the cooling conduit until a predestined temperature of the intra-abdominal surface between 32 – 23 °C has been reached.

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18) The assembly of the claim 1 to 16, characterised in that its controlling means is designed to regulate the temperature, humidity and or insufflation flow rate in the cooling conduit until a predestined temperature of the intra-abdominal surface between 23 – 12 °C has been reached.

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19) The assembly of the claim 1 to 18, characterised in that it cools the patient's body cavity or body cavity surface to a moderate hypothermia.

20) The assembly of the claim 1 to 18, characterised in that it cools the patient's body cavity or body cavity surface to a profound hypothermia

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21) The assembly of the claims 1 to 20, characterised in that the fluid outlet of the cooling conduit is are near the proximal end of the trocar (L) of an endoscopic surgery device.

22) The assembly of the claims 1 to 20, characterised in that the cooling channel is extending coaxially within the trocar (L) of an endoscopic surgery device to the distal end thereof.

23) A method to prevent or decrease post-operative adhesion formation between tissue surfaces in a body cavity, wherein the method prevents or decreases post-operative adhesion by cooling the tissue surfaces in said body cavity that is, has been or will be subjected to pneumoperitoneum and surgery, to a temperature and humidity that is effective to inhibit the formation of adhesions thereon.

24) The method of claim 23, wherein the surfaces in a body cavity or part of the surface is cooled to a moderate hypothermia.

25) The method of claim 23, wherein the surfaces in a body cavity or part of the surface is cooled to a profound hypothermia.

26) The method of the claim 23 to 25, characterised in that the temperature of the insufflation fluid and absolute humidity of the insufflation fluid is conditioned to obtain an absolute humidity of the insufflation fluid that is higher than the relative humidity at the intra-abdominal temperature together.

27) The method of claim 26, characterised in that the temperature of the insufflation fluid and absolute humidity of the insufflation fluid is conditioned to obtain an absolute humidity of the insufflation fluid that is 0.1 to 5 % higher than the intra-abdominal relative humidity.

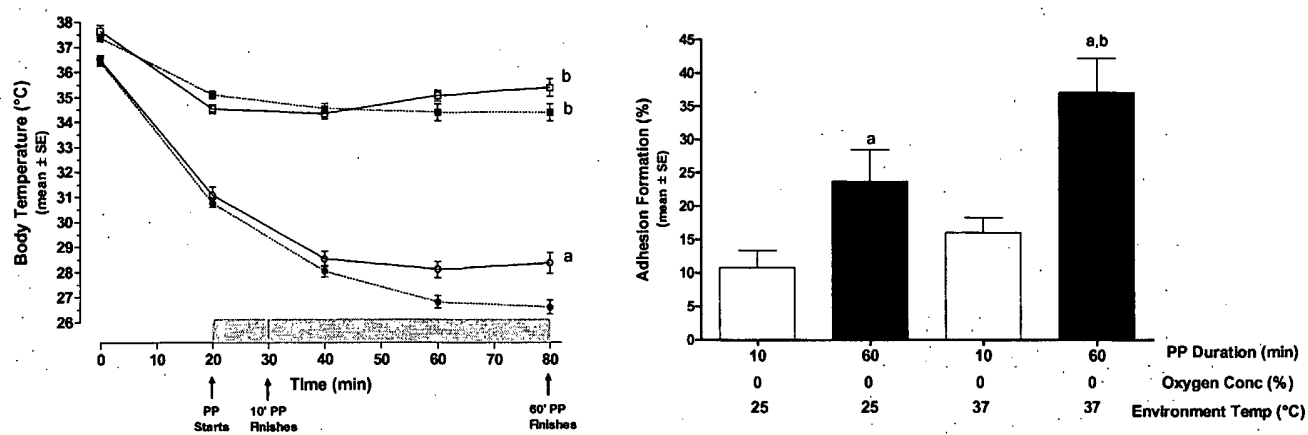


FIGURE 1

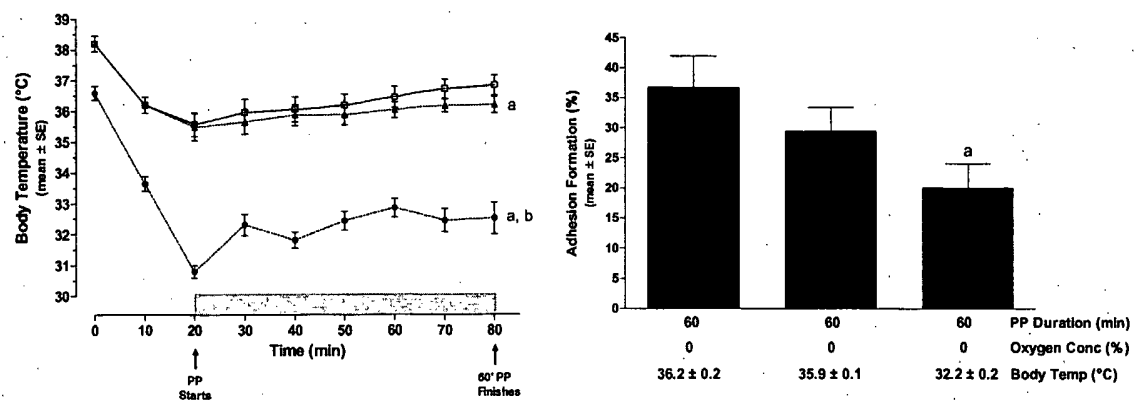


FIGURE 2

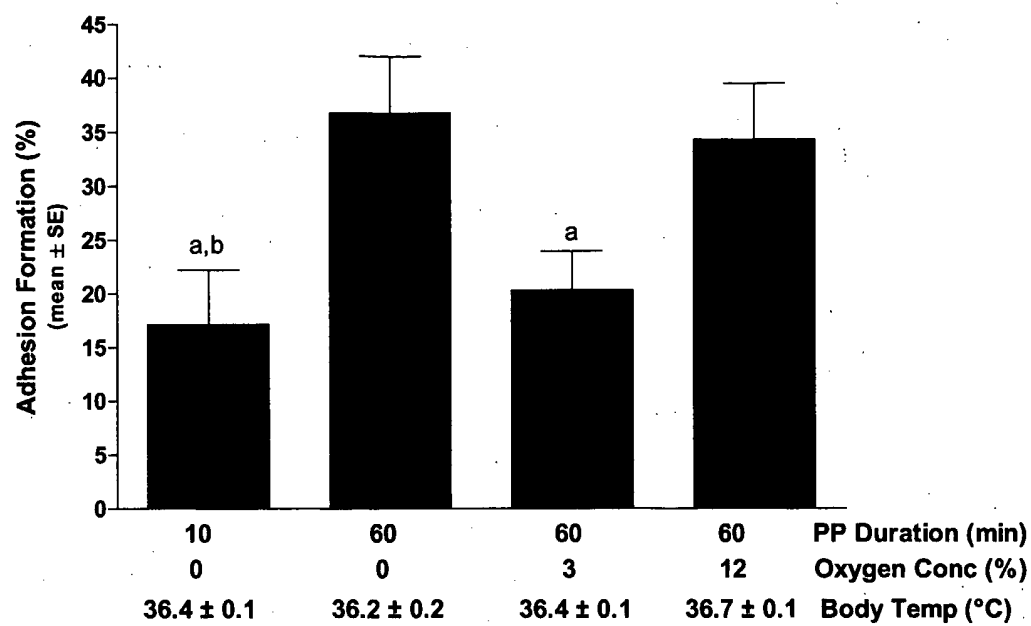


FIGURE 3

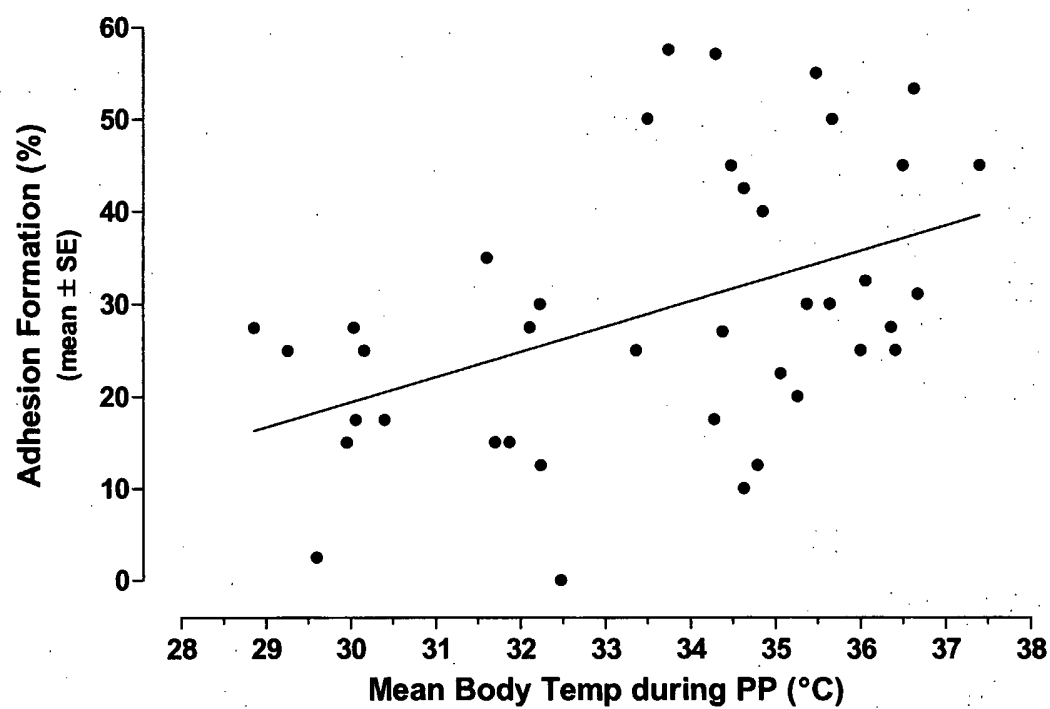


FIGURE 4

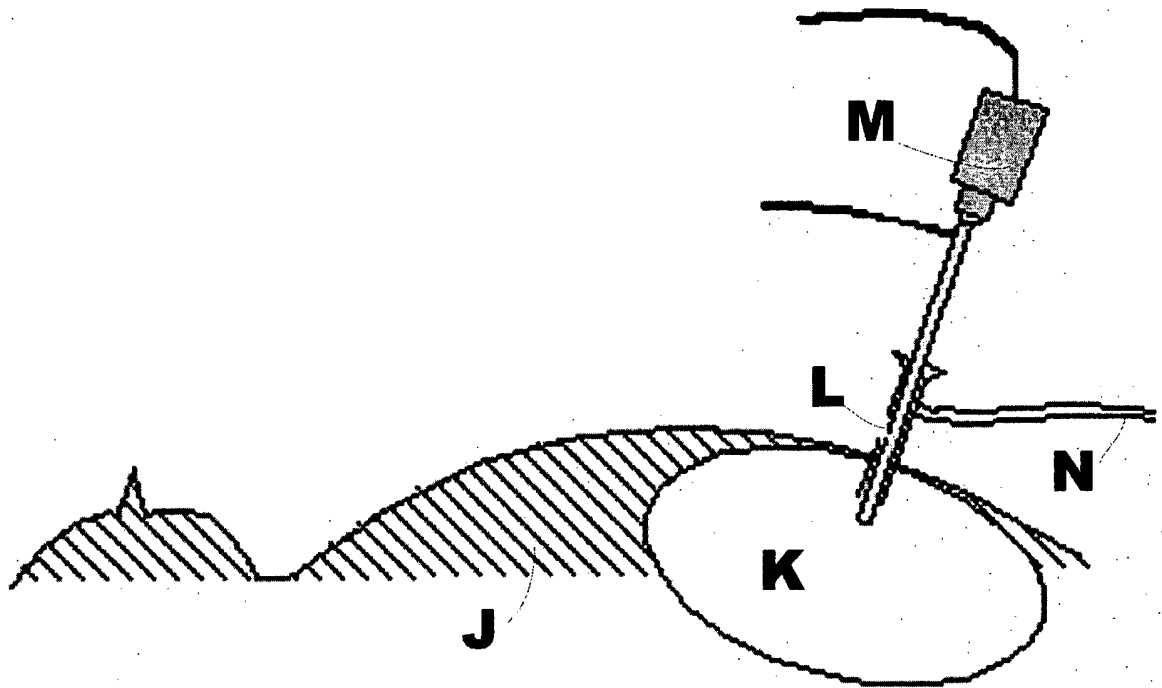


FIGURE 5

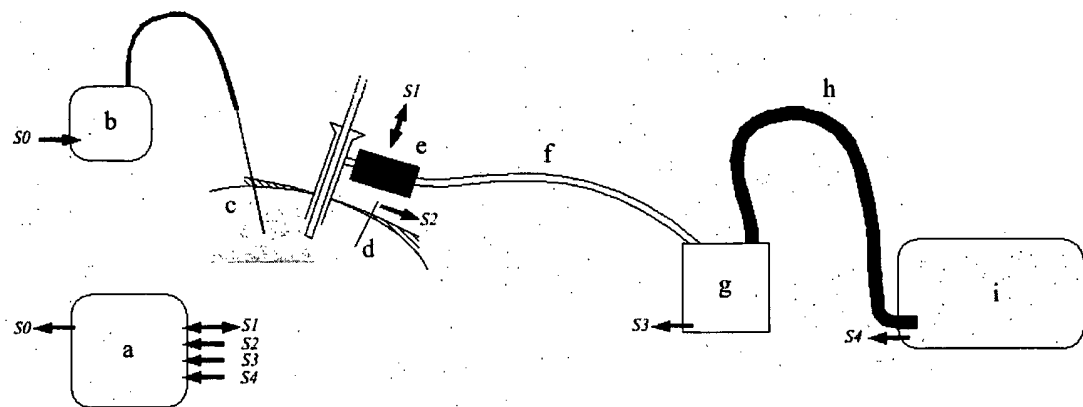


FIGURE 6

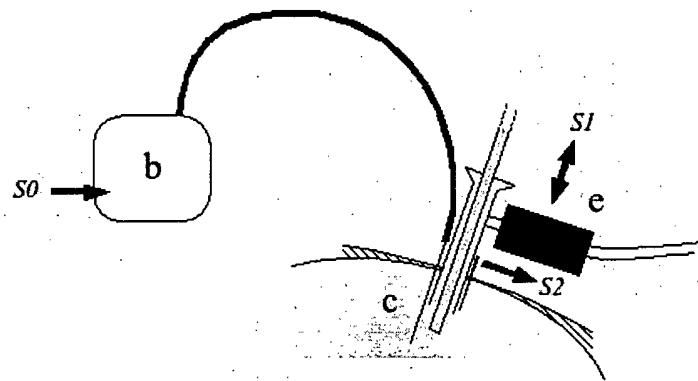
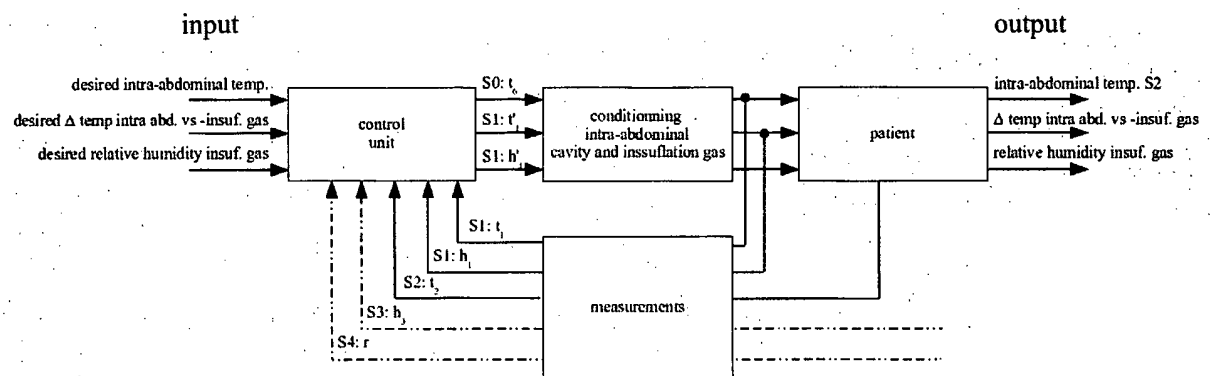


FIGURE 7



INTERNATIONAL SEARCH REPORT

In  onal Application No
PCT/BE2005/000089

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61F7/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61F A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/54682 A (NTERO SURGICAL, INC) 21 September 2000 (2000-09-21) abstract; figure 9	1-7, 17-22
Y	page 1, line 21 - page 2, line 28 page 4, line 7 - line 14 page 12, line 13 - page 13, line 20	8-16
Y	US 5 246 419 A (ABSTEN ET AL) 21 September 1993 (1993-09-21) abstract column 3, line 25 - column 6, line 29	8-10, 12-16
Y	US 2004/087934 A1 (DOBAK JOHN D ET AL) 6 May 2004 (2004-05-06) abstract; figure 6 paragraph '0078!	11
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

* & * document member of the same patent family

Date of the actual completion of the international search

31 August 2005

Date of mailing of the international search report

06/09/2005

Name and mailing address of the ISA

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Beck, E

INTERNATIONAL SEARCH REPORT

International Application No
PCT/BE2005/000089

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 98/32383 A (CRYOMEDICAL SCIENCES, INC; BAUST, JOHN, G; BAUST, JOHN, M; POTTORF, LA) 30 July 1998 (1998-07-30) page 12, line 16 - line 28 -----	10
A	US 6 338 731 B1 (LAUFER MICHAEL D ET AL) 15 January 2002 (2002-01-15) abstract column 5, line 7 - line 16 -----	1

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/BE2005/000089

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 23-27
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/BE2005/000089

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Information on patent family members

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