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Heated and Humidified CO_2 Prevents Hypothermia, Peritoneal Injury, and Intra-Abdominal Adhesions During Prolonged Laparoscopic Insufflations

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Background. **Insufflation with standard cold-dry CO_2 during laparoscopic surgery has been shown to predispose patients to hypothermia and peritoneal injury. This study aimed to compare the effect of prolonged cold-dry CO_2 insufflation with heated-humidified CO_2 insufflation (3–5 h) on hypothermia, peritoneal damage, and intra-abdominal adhesion formation in a rat model.**

Materials and methods. **A total of 160 Wistar rats were randomized to undergo no insufflation or insufflation with cold-dry CO_2 (21°C, <1% relative humidity) or heated-humidified CO_2 (37°C, 95% relative humidity) for 3, 4, or 5 h. Core body temperature was measured via rectum before and during insufflations. Peritoneal samples were taken at 6, 24, 48, and 96 h after treatments and analyzed with light microscopy and scanning electron microscopy. Intra-abdominal adhesions were evaluated 2 weeks later.**

Results. **Core body temperature significantly decreased in the cold-dry group, whereas it was maintained and increased in the heated-humidified group. Scanning electron microscopy and light microscopy studies showed intense peritoneal injury in the cold-dry CO_2 group but significantly less damages in the heated-humidified group. Increased intra-abdominal adhesion formation was observed in the cold-dry CO_2 group, while no adhesions were found in the rats insufflated with heated-humidified CO_2.**

Conclusions. **Heated-humidified CO_2 insufflation results in significantly less hypothermia, less peritoneal damage, and decreased adhesion formation as compared with cold-dry CO_2 insufflation. Heated-humidified CO_2 may be more suitable for insufflation application in prolonged laparoscopic surgery.**

Key Words: **laparoscopy; carbon dioxide; insufflation; heat; humidity.**

INTRODUCTION

In recent years, laparoscopic surgery has been increasingly applied to complex intra-abdominal procedures such as bariatric surgery and surgery for gastrointestinal malignancy. The increased complexity of laparoscopic surgery requires much longer operation time. For example, the operation time required for the laparoscopic colorectal cancer surgery is as long as 120–275 min [1, 2]. In laparoscopic pancreatodudenectomy, the operation time is even longer [3–5].

Prolonged laparoscopic surgery requires long duration and large volume gas insufflations, which raises concerns about the adverse effects of prolonged gas insufflations [6–8]. It is well known that carbon dioxide (CO_2) is the most commonly used gas for laparoscopic insufflations. However, the standard CO_2 used in current laparoscopic practice is cold-dry CO_2 (20–21°C and 0.0002% relative humidity), which is not physiological to the normal condition of the peritoneal cavity (36°C and virtually 100% relative humidity) [9]. Experimental and clinical studies of short-duration laparoscopic insufflation (<3 h) have demonstrated that cold-dry CO_2 insufflations can cause peritoneal alterations and result in numerous detrimental outcomes, including hypothermia, increased postoperative pain and narcotics usage, as well as prolonged recovery [8, 10–16]. Therefore, it is speculated that prolonged cold-dry CO_2 insufflations may result in more intense peritoneal alterations and expose patients to increased

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risk of its detrimental effects. Recently, there has been accumulating evidence that insufflation with heated-humidified CO_2 (37°C and 95% relative humidity, physiological condition) can eliminate or greatly alleviate the detrimental effects of cold-dry CO_2 insufflations [8, 11, 13, 15, 17–21]. The benefits of heated-humidified CO_2 insufflations have been reported to include less hypothermia, less postoperative pains, shortened recovery room stay, better convalescence, and less tumor spread and growth [8, 10–16, 22–24]. Accordingly, it is speculated that heated-humidified CO_2 may be able to prevent the adverse effects of prolonged cold-dry CO_2 insufflations during complex laparoscopic surgery.

The purpose of this study was to evaluate the detrimental effects of prolonged cold-dry CO_2 insufflations (>3 h) and the effectiveness of heated-humidified CO_2 in preventing those adverse effects in a rat model. Two commonly concerned areas of the detrimental effects, hypothermia and peritoneal injury, were selected for evaluation. Intra-abdominal adhesion formation, as one of the consequences of peritoneal injury, was also assessed.

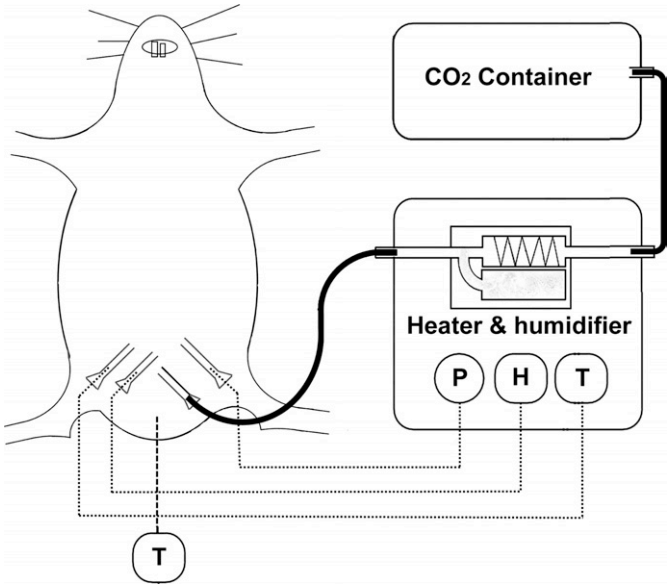

FIG. 1. Experimental setup (the rat was magnified for illustration): CO_2 was released from CO_2 container and entered into the heater and humidifier. After heating-humidifying or not, the heated-humidified or cold-dry CO_2 was insufflated into the peritoneal cavity of the rat. The intra-abdominal temperature (T), relative humidity (H), and pressure (P) were monitored and displayed on the control panel of the heater and humidifier. Core temperature was measured via rectum (T).

MATERIALS AND METHODS

Animals

A total of 160 male Wistar rats (mean weight, 275 g) were used in this study. The animals were kept under standard laboratory conditions (temperature 20–24°C, relative humidity 50–60%, 12 h light, 12 h dark), fed with laboratory diet, and allowed free access to water. The experimental protocol was approved by the Ethical Committee of the Shanghai Jiaotong University, China. All animals were handled in accordance with the Guide for Care and Use of Laboratory Animals published by the US National Institutes of Health.

Experimental Design

The rats were randomly divided into 7 groups: Groups C3, C4, C5: rats receiving cold-dry CO_2 (21°C, <1% relative humidity) insufflations for 3 h, 4 h, or 5 h, respectively ($n = 25$ each group); Groups H3, H4, H5: rats undergoing heated-humidified CO_2 (37°C, 95% relative humidity) insufflations for 3 h, 4 h, or 5 h, respectively ($n = 25$ each group); and Group N: rats receiving no gas insufflations but anesthesia alone ($n = 10$). In Groups C3, C4, C5, H3, H4, and H5, every five rats from each group were sacrificed for analysis of peritoneal injury (light microscopy and scanning electron microscopy) at 6, 24, 48, or 96 h after treatments and intra-abdominal adhesions on day 14 after treatment. Group N served as blank controls for analysis of peritoneal injury and adhesions (5 rats for each). Core temperature (preoperation, intraoperation, and postoperation) was measured via rectum in all groups.

Operation Procedures

For the rats given gas insufflations, the operation procedures were as follows. After each rat was anesthetized by using diethyl ether inhalation, it was restrained in the supine position. After shaving and cleansing with 70% alcohol, the abdominal wall of rat was lifted, and an 18-G needle (Vasocan, Penang, Malaysia) was inserted at lower midline and connected to CO_2 insufflator. After establishment of pneumoperitoneum, three other needles were inserted in the left lower quadrant, the middle midline, and the right lower quadrant, respectively. They were correspondingly connected to pressure, humidity, and thermal detectors (Fig. 1). The upper abdominal wall was kept intact during operations for further morphological investigations. Heated-humidified or cold-dry CO_2 was insufflated into the peritoneal cavity at 9 mmHg with a flow rate of 300 mL/min. The heated-humidified CO_2 and cold-dry CO_2 were provided by a newly developed CO_2 heater and humidifier device (patent protected by State Intellectual Property Office of China, No. 2006200477736). The device was equipped with a control system and free temperature/humidity probe at the end of transfer hoses, which regulated the temperature/humidity of the gas insufflated into the peritoneal cavity and guaranteed high stability of them (±0.3°C/±5% relative humidity). The device also included a control panel that displayed the intra-abdominal temperature (T), relative humidity (H), and pressure (P) in real-time (Fig. 1). During the operations, the rats were wrapped with a heating blanket to maintain normothermia (pilot study showed serious decrease of body temperature without heating blanket). After treatment, all rats were allowed to recover from anesthesia and were returned to their cages.

Core Temperature

Core temperature of the rat was measured via rectal thermometry by using HP 34970A Data acquisition-Switch unit (Hewlett Packard, Palo Alto, CA) (Fig. 1). It was monitored continuously and recorded every 20 min. Manifestations associated with hypothermia (such as shivering) were also recorded.

Light Microscopy

After the rats were sacrificed, the abdominal wall was immediately opened by a midline incision. Peritoneum and underlying muscles of the anterior and upper abdomen were immediately resected and fixed in 10% formalin. Then the specimens were embedded in

paraffin and sectioned with microtome. The sections (5 J.m) were stained with hematoxylin and eosin. Images were obtained using Olympus IX71 light microscope (Olympus, Japan) with digital camera output (Nikon Digital Sight DS-U1, Nikon, Tokyo, Japan). All of the peritoneal specimens were analyzed by an independent observer who was blind to the experimental design. Structural changes, cellular damages, and inflammatory response were assessed and compared between groups.

Scanning Electron Microscopy

Peritoneal samples of anterior and upper abdomen were obtained as described above. After resection, the specimens were immediately fixed in 2.5% glutaraldehyde in 0.1 M phosphate-buffered saline (pH 7.4) for 6 h. After fixation, the specimens were rinsed with 0.1 M phosphate-buffered saline (pH 7.3) for 30 min. Then they were post-fixed in 1% OsO_4 in 0.1 M sodium phosphate buffer (pH 7.3) for 2 h. After dehydration in graded alcohol (30 –50 –70 – 80 –95–100%, 15 min for each), the specimens were impregnated in hexamethyldisilazane and air-dried. Finally the dried specimens were mounted on stubs and sputter-coated with gold. All peritoneal specimens were examined with a QUANTA-200 scanning electron microscope (Philips, Eindhoven, Netherlands) by a blinded independent observer. The peritoneal surface was examined at five random fields per specimen for changes of mesothelial cells (alterations of microvilli, bulging-up, desquamation, and intercellular clefts) and visibility of the basal lamina (denudation of the basal lamina).

Intra-Abdominal Adhesions

Intra-abdominal adhesions were evaluated 2 weeks after treatments by an independent observer who was blinded to the experimental design. The peritoneum was examined and the adhesions were scored with modified method primarily described by Binda *et al.* [17]. The extent of adhesions was scored as follows: First, the extent, type, and tenacity of the adhesions were scored individually: extent (0: no adhesions; 1: 1–25%; 2: 26 –50%; 3: 51–75%; 4: 76 –100% of the injured surface involved), 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). Then the extent, type, and tenacity score were added up and the sum was the total score of intra-abdominal adhesions.

Statistical Analysis

Statistical analysis was performed using SPSS version 11.0 (SPSS Inc., Chicago, IL). Data were presented as mean ± SD. Differences between groups were evaluated with Student's *t*-test and one-way ANOVA as appropriate. Pearson's correlation analysis was performed to assess the relationship between the decrease of core temperature and the duration of insufflations. A P value less than 0.05 was considered significant.

RESULTS

All animals survived the study. There were no differences among all groups in body weight and induction of anesthesia. The room temperature during the experiments was 23.5 ± 0.3°C.

Core Temperature

Before treatments, the core temperature did not differ among all groups and the mean baseline measurement was 35.3 ± 0.3°C. After treatments, the core temperature of rats given cold-dry CO_2 insufflations for 3, 4, and 5 h significantly fell by 2.32 ± 0.2°C, 2.84 ± 0.14°C, and 3.11 ± 0.22°C, respectively ($P = 0.011$, $P = 0.003$, and $P < 0.001$, correspondingly). The core temperature drop was treatment duration-dependent ($P = 0.009$, $r = 0.86$). Due to remarkable hypothermia, shivering occurred in 7/25, 11/25, and 11/25 rats in groups C3, C4, and C5, respectively. In rats receiving heated-humidified CO_2 insufflations, the core temperature was maintained and increased by 1.31 ± 0.11°C, 1.4 ± 0.15°C, and 1.39 ± 0.18°C in groups H3, H4, and H5, respectively. No shivering was observed. The rats recovered from anesthesia and returned to normal diet and activity much quicker than those rats receiving cold-dry CO_2 insufflation. The changes of core temperature over time are shown in Fig. 2 (representatively illustrated by groups receiving gas insufflations for 5 h).

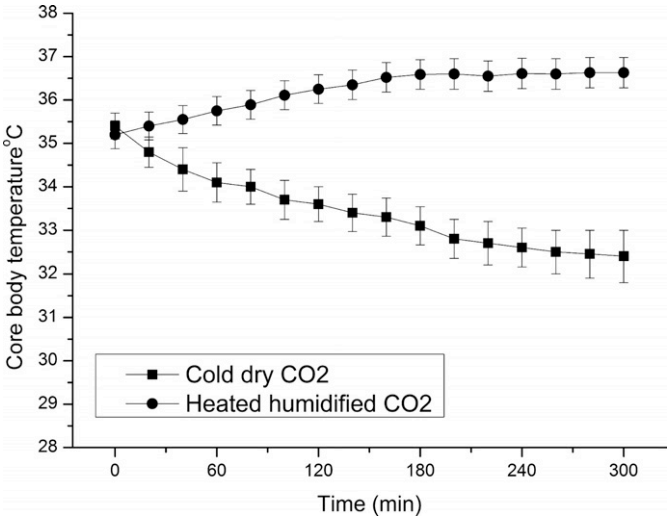

FIG. 2. Changes of core temperature (°C) in rats given cold-dry or heated-humidified CO_2 insufflations for 5 h. Data points represent mean ± SD for each group.

Light Microscopy

Light microscopic examinations revealed that peritoneal injuries of rats given cold-dry CO_2 insufflations were much more serious than those of rats insufflated with heated-humidified CO_2. In rats receiving cold-dry CO_2 insufflations, extensive desquamation of mesothelial cells and disruption of underlying connective tissue in a duration-dependent manner were found 6 h after the treatments (Fig. 3B). In group C4 and C5, the peritoneal surface was almost entirely denuded without mesothelial cells (Fig. 3B). At 24 and 48 h after insufflation, inflammatory cells infiltrated into full-thickness peritoneum, which indicated a significant inflammatory response (Fig. 3D). At 96 h after treatment, most of (group C3) or approximately the entire (groups C4, C5) damaged area remained unrecovered and the peritoneum consisted of only thickened connective tissue without mesothelial cells (Fig. 3E). By con-

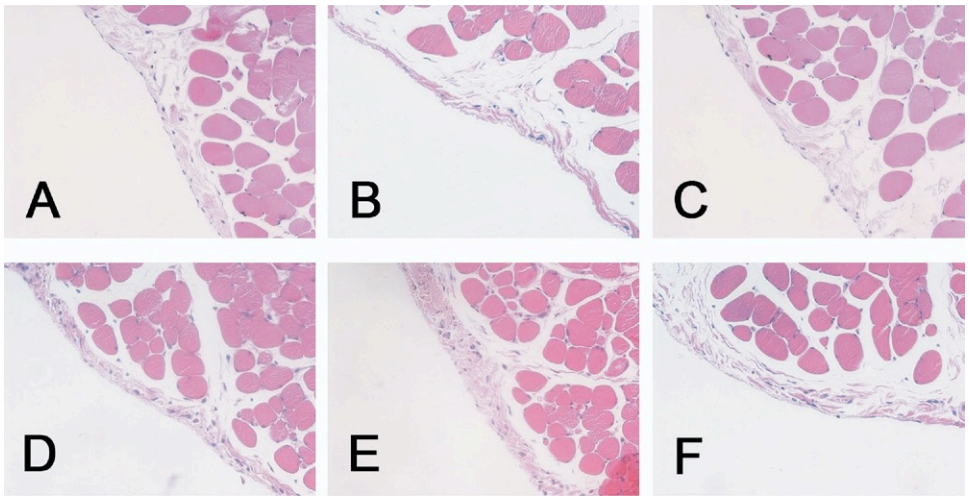

FIG. 3. Light microscopic analysis of peritoneal alterations (HE, X200) (exemplified by rats exposed to cold-dry or heated-humidified CO_2 insufflations for 4 h). (A) Normal peritoneum; (B) 6 h after cold-dry CO_2 insufflation; (C) 6 h after heated-humidified CO_2 insufflation; (D) 24 h after cold-dry insufflation; (E) 96 h after cold-dry CO_2 insufflation; (F) 96 h after heated-humidified CO_2 insufflation. (Color version of figure is available online.)

trast, heated-humidified CO_2-treated rats had much less peritoneal damages. Extensive detachment of the mesothelial cells and obvious inflammatory response were not found, only a sporadic small area of desquamation was observed in rats subjected to HH-CO_2 for 4–5 h (groups H4, H5) (Fig. 3C). At 96 h after insufflation, entire (groups H3, H4) and most of (groups H5) the damaged peritoneum recovered and returned to normal (Fig. 3F).

Scanning Electron Microscopy

Scanning electron microscopy examination confirmed the findings from light microscopy and clearly showed the alterations of peritoneal surface. Under a scanning electron microscope, normal peritoneum was covered by a continuous layer of mesothelial cells with dense microvilli, and no basal lamina were visible (Fig. 4A and B). In rats receiving cold-dry CO_2 insufflations, 6 h after the treatments, the mesothelial cells extensively desquamated from the peritoneal surface and the basal lamina was clearly seen (>90% area of peritoneal surface was involved) (Fig. 4D, E, and F). In groups C4, C5, uncovered basal lamina was seen nearly in the entire peritoneum and the basal lamina became disrupted and loose due to a long period of evaporation and desiccation (Fig. 4E and F). Obvious inflammatory response was observed 24 h later; numerous macrophages and lymphocytes gathered on the basal lamina as shown in Fig. 4J. At 96 h after the insufflations, most of (group C3) or approximately the entire (groups C4, C5) damaged area remained denuded without mesothelial cells (Fig. 4K). By contrast, for rats given heated-humidified CO_2 insufflations, the peritoneal injuries were significantly less serious. In group H3, detachment of mesothelial cells at 6 h after treatments was slight (Fig. 4G). However, the mesothelial cells bulged up with prominent alterations of microvilli (including microvilli shortening, reduction in number, and disappearance). The intercellular clefts became visible and the basal lamina was partially seen (Fig. 4C and G). In groups H4 and H5, massive desquamation and denuded basal lamina were not found, but the denuded area involved no more than 50% area of peritoneal surface (Fig. 4H and I). At 48 h after treatments, the damaged peritoneum began to recovery. The mesothelial cells returned to normal and regenerated to cover the denuded area. By 96 h after CO_2 insufflations, the total (group H3) or most area of (groups H4, H5) damaged peritoneum recovered to normal (Fig. 4L).

Intra-Abdominal Adhesions

Peritoneal injury may result in or facilitate intra-abdominal adhesion formation. The peritoneal cavity of rats was explored 2 weeks after the procedures. The intra-abdominal adhesions only occurred in rats given cold-dry CO_2 insufflations for 4–5 h. One rat in group C4 and two rats in group C5 developed intra-abdominal adhesions after treatments. The adhesions at port sites were intense and seen in both groups (Fig. 5A). The adhesions at nonoperative sites were mild, filmy, and easily dissected, and they were seen in only one rat, which was given insufflation for 5 h (Fig. 5B). The adhesion scores are listed in Table 1.

DISCUSSION

In recent years, the laparoscopic approach has been increasingly applied to complex abdominal surgery. Nevertheless, the effects of prolonged gas insufflations

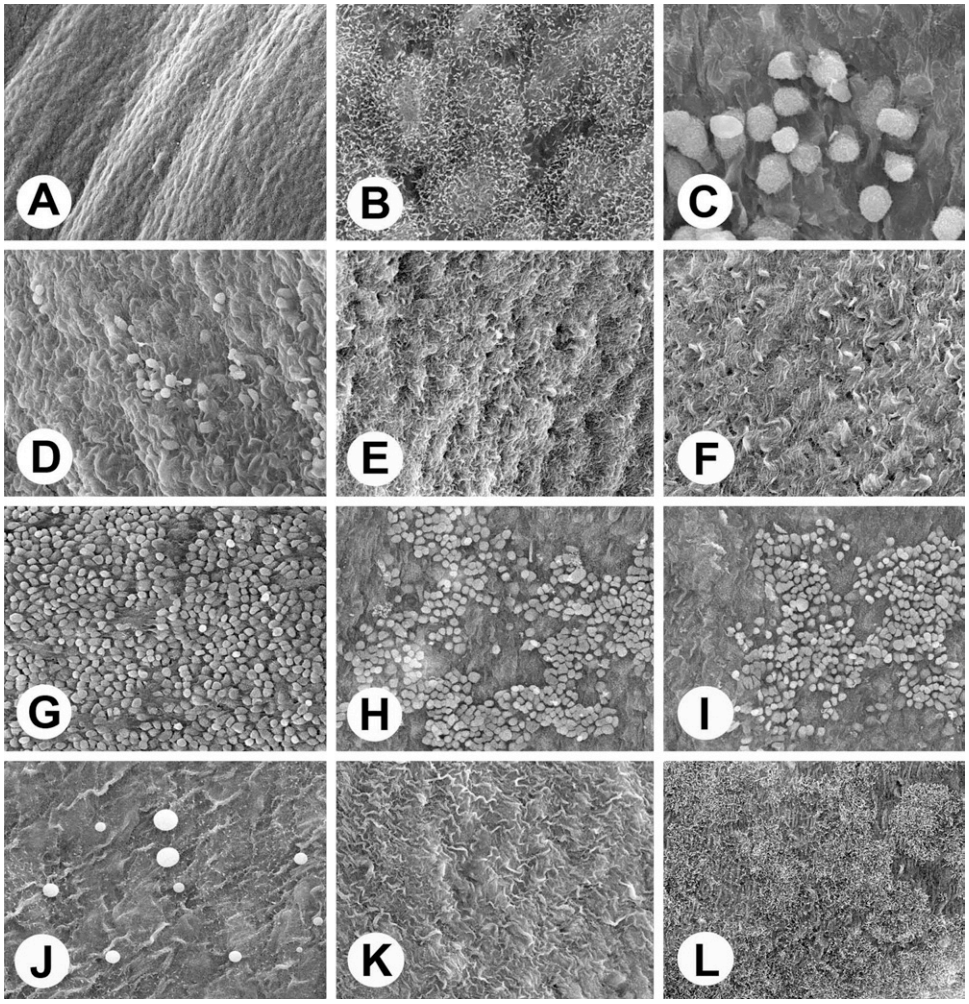

FIG. 4. Scanning electron microscopic analysis of peritoneal alterations. (A, B) Normal peritoneum (X200, X3000); (C) damaged mesothelial cells and denuded basal lamina (X3000); (D, E) 6 h after cold-dry CO_2 insufflations for 3–5 h (X700); (G-I) 6 h after heated-humidified CO_2 insufflations for 3–5 h (X700); (J) 24 h after cold-dry CO_2 insufflations for 4 h (X1300); (K) 96 h after cold-dry CO_2 insufflations for 4 h (X700); (L) 96 h after heated-humidified CO_2 insufflations for 4 h (X700).

(>3 h) used in complex laparoscopic surgery on core temperature and peritoneum remain unknown. This experimental study showed that prolonged cold-dry CO_2 insufflations (3–5 h) resulted in significant hypothermia, serious peritoneal injury, and increased intra-abdominal adhesion formation. Insufflations with heated-humidified CO_2 eliminated or greatly alleviated the detrimental effects of cold-dry CO_2 insufflations.

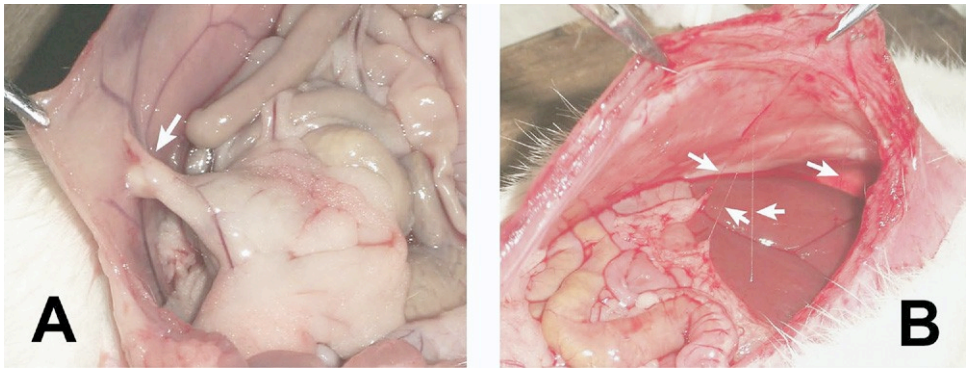

FIG. 5. Intra-abdominal adhesions (white arrow). (A) Adhesion at port site in rat receiving cold-dry CO_2 insufflation for 4 h; (B) Adhesion at right upper quadrant in rat given cold-dry CO_2 insufflation for 5 h. (Color version of figure is available online.)

TABLE 1

Intra-Abdominal Adhesion Scores of Rats 2 Weeks After Treatments (mean ± SD)

	Intra-abdominal adhesion scores		
Gas insufflations	3 h	4 h	5 h
Cold-dry	0	1.8 ± 4.02	2.6 ± 3.97
Heated-humidified	0	0	0

Hypothermia is one of the most concerned areas of the detrimental effects of standard cold-dry CO_2 insufflations. Cold-dry CO_2 insufflation can cause thin-film evaporation of peritoneal surface and decreases core temperature [9, 18, 25–30]. Clinical and experimental studies of short-duration laparoscopic insufflation (<3 h) have demonstrated that cold-dry CO_2 could result in significant decrease of core temperature and the decrease was correlated with duration of insufflation and total volume of gas insufflated [8, 10, 12–14, 19, 23, 25, 26, 29, 31, 32]. Our results of prolonged gas insufflations (3–5 h) were consistent with the findings of those studies. Prolonged cold-dry CO_2 insufflations resulted in significant hypothermia and the decrease of core temperature was roughly proportional to the duration of insufflation. Hypothermia is known to be associated with numerous deleterious effects, including increased susceptibility to wound infection, hypokalemia, impaired myocardial function, respiratory depression, disruption of coagulation, and prolonged postoperative recovery [31, 33–41]. It has been demonstrated that heated-humidified CO_2 can eliminate or greatly alleviate hypothermia [8, 10, 12, 13, 15, 19, 20, 25, 26]. Our results of prolonged heated-humidified CO_2 insufflations (3–5 h) were similar to those observed in studies of short-duration insufflations (<3 h). Heated-humidified CO_2 was also effective in preventing hypothermia during prolonged gas insufflations. Furthermore, it could not only maintain but also increase the core temperature.

Peritoneal injury is another reported adverse effect of cold-dry CO_2 insufflation. Cold-dry CO_2 insufflation has been demonstrated to cause peritoneal desiccation, damage of peritoneal surface, and subsequent inflammatory response, which contribute to the visible clinical findings such as increased postoperative pain and prolonged recovery [9–11, 18, 19, 21, 29, 41, 42]. The extent of peritoneal damage increased with the duration of gas insufflations [18]. In studies regarding short-duration insufflations, the peritoneal damage was reported to be moderate, transient, and reversible [43–45]. Suematsu *et al.* [44] and Volz *et al.* [45] demonstrated characteristic ultrastructural changes of peritoneal surface after cold-dry CO_2 insufflations for 30–60 min in a mice model. The mesothelial cells regenerated and the peritoneum recovered to normal 72–96 h later. As to procedures of relatively long duration (2 h), Hazebroek *et al.* [19] and Erikoglu *et al.* [11] reported more intense peritoneal damages, but they did not mention the recovery of the damaged peritoneum. Our results of prolonged insufflations showed that prolonged cold-dry CO_2 insufflations (3–5 h) resulted in more serious peritoneal damages and the damages appeared to be irreversible. Heated-humidified CO_2 is reported to be able to eliminate or greatly alleviate the peritoneal damages from cold-dry CO_2 [11, 18, 21]. Erikoglu *et al.* [11] reported that heated-humidified CO_2 resulted in significantly less peritoneal injury than cold-dry CO_2 after insufflations for 2 h. Our results of prolonged insufflations (3–5 h) were similar to their findings. Heated-humidified CO_2 greatly alleviated the peritoneal damages and facilitated the recovery of damaged peritoneum (entire or most areas of peritoneum recovered 96 h after treatments). Nevertheless, unlike the results of those studies regarding short-duration gas insufflations, our study showed that peritoneal injury still occurred, although the heated-humidified CO_2 insufflation was used. We speculated that the peritoneal injury may be attributable to prolonged CO_2 insufflation-induced peritoneal acidosis and hypoxia, which was reported to be responsible for peritoneal damages [45–51].

Peritoneal injury was reported to facilitate intra-abdominal adhesion formation and tumor implantation [9, 10, 52–56]. The intra-abdominal adhesions after gas insufflations were discussed in this study. In procedures of short duration, it has been demonstrated that cold-dry CO_2 insufflation could cause peritoneal injury and facilitate the adhesion formation [17, 18]. Molinas *et al.* [50] and Binda *et al.* [57] reported that intra-abdominal adhesions increased with the duration of gas insufflation. It was reported that heated-humidified CO_2 could eliminate the factors contributing to cold-dry CO_2 insufflation-induced adhesion formation and prevent it [17, 18]. Binda *et al.* [17] demonstrated that peritoneal desiccation increased adhesion formation and the desiccation-enhanced adhesions could be prevented by using humidified gas. Our results of prolonged insufflations were similar to their findings. The prolonged cold-dry CO_2 induced intra-abdominal adhesions and the adhesions significantly increased with the duration of insufflations. No adhesions (nonoperation sites) were observed when the heated humidified CO_2 was used for insufflation. The adhesion formation was prevented by heated-humidified CO_2. The question about tumor implantation after peritoneal injury was left unanswered in this study. The serious peritoneal injury after prolonged cold-dry CO_2 insufflations may increase the risk of peritoneal metastasis and port site metastasis in laparoscopic cancer surgery. Whether the heated-humidified CO_2 can prevent them is unknown, although it was reported to reduce tumor growth and spread after short-duration

cold-dry CO_2 insufflation [23, 24, 58]. Further investigations into this area are warranted.

A limitation of this study is the relative small sample size. To offset this disadvantage, we apply the following methodology as rigorously as possible to guarantee unbiased evaluations. All groups were well matched and all procedures were performed with the same style by one independent operator who was blinded to the experimental design. All observers were also blinded to the experimental design. Therefore the only difference between groups is the treatment under investigation.

In summary, this study demonstrates that prolonged standard cold-dry CO_2 insufflation can result in significant hypothermia, serious peritoneal injury, and increased intra-abdominal adhesions. Heated-humidified CO_2 can eliminate or greatly alleviate the detrimental effects of cold-dry CO_2. These results suggest that heated-humidified CO_2 may be more suitable for prolonged laparoscopic surgery. Further research in large animals is needed and now underway in our institute. The results will be available in the near future.

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