ORIGINAL ARTICLE

High Intra-abdominal Pressure Increases Plasma Catecholamine Concentrations During Pneumoperitoneum for Laparoscopic Procedures

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Background: Laparoscopic procedures are associated with several complications, such as hemodynamic, respiratory, and endocrine complications. In our previous clinical study, plasma epinephrine and norepinephrine concentrations remained unchanged after the insertion of a Veress needle, but increased significantly immediately after insufflation with carbon dioxide into the peritoneum. The mechanisms for this increase are unknown.

Objective: To investigate whether gas insufflation during pneumoperitoneum affects plasma catecholamine concentrations during laparoscopic procedures.

Design: Experimental study in pigs.

Main Outcome Measures: The plasma concentrations of epinephrine and norepinephrine were measured in the pigs before and after pneumoperitoneum. The mean arterial pressure, heart rate, cardiac output, and arterial blood gas levels were measured, and the systemic vascular resistance was calculated.

Intervention: Air, nitrous oxide, or carbon dioxide were insufflated in turn into the peritoneal cavity of supine pigs. Thereafter, carbon dioxide was insufflated into the peritoneal cavity while the pig was in the left lateral decubitus position, and then in the right lateral decubitus position. Measures were performed before pneumoperitoneum and at the intra-abdominal pressures of 10 mm Hg and 20 mm Hg. One hour of resting time was allowed between each procedure.

Results: As compared with baseline values, the plasma concentrations of epinephrine and norepinephrine remained unchanged at 10 mm Hg but increased significantly at 20 mm Hg regardless of the gas used for the pneumoperitoneum ($P<.05$). The type of gas and differences in the position of the animals had no effect on the plasma epinephrine and norepinephrine concentrations.

Conclusions: Excessive intra-abdominal pressure, but not the type of gas or body position, increases plasma catecholamine concentrations during the insufflation of gas into the abdominal cavity. Therefore, excessive insufflation of the pneumoperitoneum should be avoided.

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LAPAROSCOPIC surgery is a relatively noninvasive therapy. The efficacy of urological laparoscopic procedures such as pelvic lymphadenectomy, simple nephrectomy, and adrenalectomy has been confirmed.[1,2] However, these procedures require a pneumoperitoneum, which may cause cardiovascular and respiratory complications.[3,4] Laparoscopic procedures also affect endocrine and metabolic functions, such as increases in the serum cortisol, prolactin, and glucose concentrations after cessation of the pneumoperitoneum.[5]

Previously, we found that the plasma concentrations of epinephrine and norepinephrine remained unchanged after the insertion of a Veress needle but increased significantly immediately after creation of pneumoperitoneum at 15 mm Hg of intra-abdominal pressure (IAP) in laparoscopic surgery.[6] This increase in the plasma catecholamine concentrations may be detrimental, particularly in elderly patients or in patients with pheochromocytoma.[7]

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The reason for this increase is not known. The degree of the IAP, the type of insufflation gas, the position of the patient, and the concentrations of blood carbon dioxide are possible contribu-

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MATERIALS AND METHODS

ANIMAL PREPARATION

All experiments were performed in accordance with the guidelines for the care and use of laboratory animals at Kansai Medical University, Osaka, Japan. Five female hybrid pigs weighing 17 to 20 kg (mean±SD, 18.2±1.8 kg) were used.

Anesthesia was induced with ketamine (20-25 mg/kg) injected intramuscularly. After 1% to 2% isoflurane had been given for 10 minutes, tracheotomy was performed. Muscle relaxation was accomplished with vecuronium and anesthesia was maintained with 1% isoflurane in a mixture of oxygen and air. Ventilation was controlled with a tidal volume of 10 mL/kg and respiratory rate of 50/min.

The animals were placed on an operating table in the supine position and the limbs were fixed. A catheter was inserted into the common carotid artery and a pulmonary artery catheter was inserted through the right internal jugular vein. Lactated Ringer solution was given intravenously at a rate of 20 mL/kg per hour. Electrocardiographic data, arterial blood pressure, and the end-tidal carbon dioxide tension were monitored. Hypothermia was prevented by heating the operating table. A trocar for the laparoscopy was placed into the peritoneal cavity at the middle of the abdomen using the Hasson technique,[8] and a 6F pigtail catheter for the cystostomy was also inserted.

One hour after these procedures, insufflation of the peritoneal cavity was initiated after the confirmation of hemodynamic stability. An automatic insufflator (model A5645.1, Olympus, Tokyo, Japan) was used to maintain the predetermined pressure. The flow rate of the gas was adjusted at 1.0 L/min for the first minute, and then raised to 9.0 L/min thereafter.

PROTOCOL

The following factors that might have influenced the plasma catecholamine concentration were assessed: (1) the type of insufflation gas, (2) the IAP during pneumoperitoneum, and (3) body position during pneumoperitoneum.

Air, nitrous oxide, or carbon dioxide was insufflated into the peritoneal cavity of each pig in turn. Initially, air was introduced into the peritoneal cavity until the IAP reached 10 mm Hg (IAP10). The IAP was maintained at IAP10 for 5 minutes. Insufflation pressure was increased until an IAP of 20 mm Hg (IAP20) was reached. The pressure was held at IAP20 for the next 5 minutes, and then the intraperitoneal gas was completely expelled. One hour of resting time was allowed between each procedure. Pneumoperitoneum using carbon dioxide was also performed in these animals while they were in the left and then the right lateral decubitus positions.

Therefore, this study was performed with the following 5 combinations of insufflation gas and operative position for each pig: air in the supine position, nitrous oxide in the supine position, carbon dioxide in the supine position, carbon dioxide in the left lateral decubitus position, and carbon dioxide in the right lateral decubitus position.

HORMONAL MEASUREMENTS

Arterial blood samples were collected before insufflation, at IAP10, and at IAP20. The blood was collected into tubes containing ethylenediaminetetraacetic acid (1 mg/mL), which were placed into an ice-chilled container. The tube was then centrifuged at 3000 rpm for 5 minutes at 4°C. Plasma was obtained, and epinephrine and norepinephrine concentrations were measured by high-pressure liquid chromatography (model HLC-725CA, Tohsoh Co, Tokyo).

RESPIRATORY AND CIRCULATORY MEASUREMENTS

The mean arterial pressure and heart rate were measured and the arterial blood gas was analyzed before insufflation (baseline), at IAP10, and at IAP20. The cardiac output was measured using the thermodilution technique and a microprocessor (model REF-1, Edwards Laboratory, Chicago, Ill). We also calculated the systemic vascular resistance.

STATISTICAL ANALYSIS

The results were expressed as mean (±SD). Variations within a single group were tested by 1-way repeated-measures analysis of variance (ANOVA) and a Fisher post hoc test. Statistical differences in the phase-dependent variables among different groups were determined by 1-way factorial ANOVA and multicomparison tests. $P<.05$ was considered to be statistically significant.

tory factors. We therefore studied the effects of these possible factors on the hemodynamics and plasma catecholamine concentrations in pigs during a pneumoperitoneum.

RESULTS

There were no significant differences in the concentrations of epinephrine and norepinephrine at baseline between any of the groups (**Table**, **Figure 1**, and **Figure 2**) (1-way factorial ANOVA).

Neither plasma epinephrine nor norepinephrine concentrations changed significantly from their baseline values as compared with those at IAP10. However, an increase to IAP20 significantly increased the plasma catecholamine concentrations in most groups.

The Pa_{CO_2} was increased during insufflation only in the groups using carbon dioxide as insufflation gas. The mean arterial pressure remained unchanged in the supine groups, but increased in the lateral position groups at both IAP10 and IAP20 (**Figure 3**). The cardiac output also increased, but not statistically significantly, in all groups at IAP10. The cardiac output at IAP20 decreased significantly in all groups except the air–supine position group as compared with the cardiac output at IAP10 (**Figure 4**). The heart rate did

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Plasma Catecholamine Levels Before the Pneumoperitoneum (Baseline), at IAP10, and at IAP20*

Measurement	Air/S	N_2O/S	CO_2/S	CO_2/L	CO_2/R
Epinephrine					
Baseline	124±82	92±46	113±76	41±25	84±89
IAP10	67±34	123±109	78±44	63±36	79±65
IAP20	285±221†	213±128‡	189±109†‡	199±78†§	151±116
Norepinephrine					
Baseline	109±72	96±56	109±73	97±81	103±87
IAP10	141±97	121±67	118±82	109±89	147±135
IAP20	213±163	218±156‡‖	225±175‡‖	153±100†§	182±219

*IAP10 indicates an intra-abdominal pressure of 10 mm Hg; IAP20, intra-abdominal pressure of 20 mm Hg; air/S, animals insufflated with air while in the supine position; N_2O/S, animals insufflated with nitrous oxide while in the supine position; CO_2/S, animals insufflated with carbon dioxide while in the supine position; CO_2/L, animals insufflated with carbon dioxide while in the left lateral decubitus position; and CO_2/R, animals insufflated with carbon dioxide while in the right lateral decubitus position. Values are mean±SD (pg/mL), N=5.

†P<.01 vs IAP10.

‡P<.05 vs baseline.

§P<.01 vs baseline.

‖P<.05 vs IAP10.

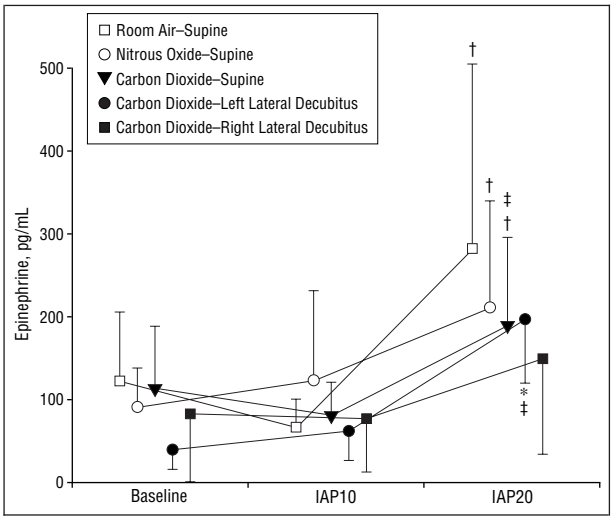

Figure 1. *Plasma epinephrine concentrations. At an intra-abdominal pressure of 20 mm Hg (IAP20), the epinephrine concentration in all groups except for the carbon dioxide–right lateral decubitus position group increased significantly. Asterisk indicates* P<.01 *vs baseline; dagger,* P<.05 *vs baseline; and double dagger,* P<.01 *vs an intra-abdominal pressure of 10 mm Hg (IAP10).*

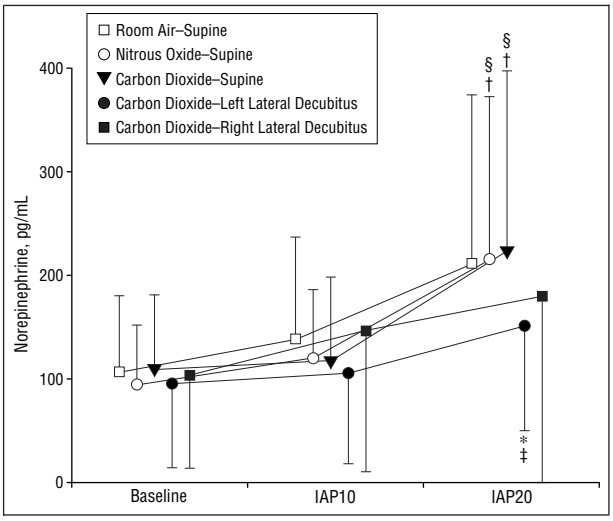

Figure 2. *Plasma norepinephrine concentrations. At an intra-abdominal pressure of 20 mm Hg (IAP20), the norepinephrine concentration increased significantly in 3 groups. Asterisk indicates* P<.01 *vs baseline; dagger,* P<.05 *vs baseline; double dagger,* P<.01 *vs an intra-abdominal pressure of 10 mm Hg (IAP10); and section mark,* P<.05 *vs IAP10.*

not change significantly in any of the groups at either IAP10 or IAP20. The systemic vascular resistance increased at IAP20 in the nitrous oxide–supine group, the carbon dioxide–supine group, and the carbon dioxide–right lateral decubitus group as compared with values at IAP10 (**Figure 5**).

COMMENT

There were no significant differences in the plasma catecholamine concentrations while using the 3 different types of insufflation gas or among the different positions during the pneumoperitoneum. In addition, there were no significant differences in the epinephrine or norepinephrine concentrations in any of the groups at IAP10. In contrast, both plasma epinephrine and norepinephrine concentrations increased significantly at IAP20. Therefore, the most likely reason for this increase in the plasma catecholamine concentrations is an increased IAP.

Trauma, circulatory failure, hypoxia, hypercapnia, and major surgical stress all increase catecholamine concentrations.[9-11] However, catecholamine concentrations remained unchanged at 1 hour after a minor surgical stress, such as inguinal hernia repair.[11] Because a tracheotomy, the insertion of a trocar, and a cystostomy may all induce an increase in plasma catecholamine concentrations as a result of injury to the skin or peritoneum, we allowed a 1-hour rest after preparation before initiating the pneumoperitoneum. We also used a heated operating table to prevent laparoscopic hypothermia.[12]

The effects of the inhaled anesthetic agent isoflurane on catecholamine release are controversial.[13,14] Ket-

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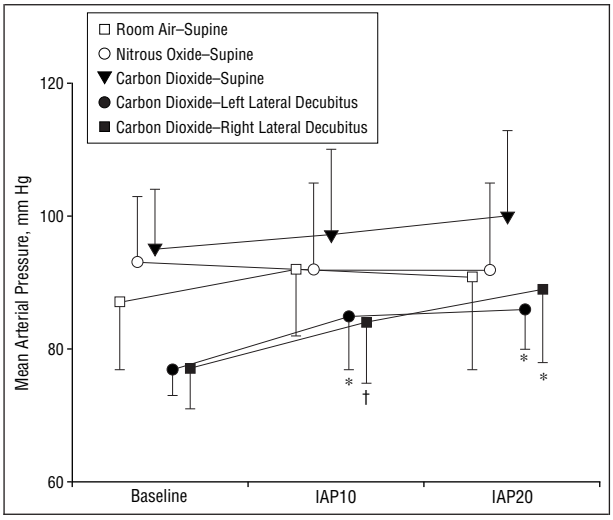

Figure 3. *Fluctuations in the mean arterial pressure. The mean arterial pressure for the carbon dioxide–left lateral decubitus and carbon dioxide–right lateral decubitus groups increased significantly at an intra-abdominal pressure of 20 mm Hg (IAP20). IAP10 indicates intra-abdominal pressure at 10 mm Hg; asterisk,* P<*.01 vs baseline; and dagger,* P<*.05 vs baseline.*

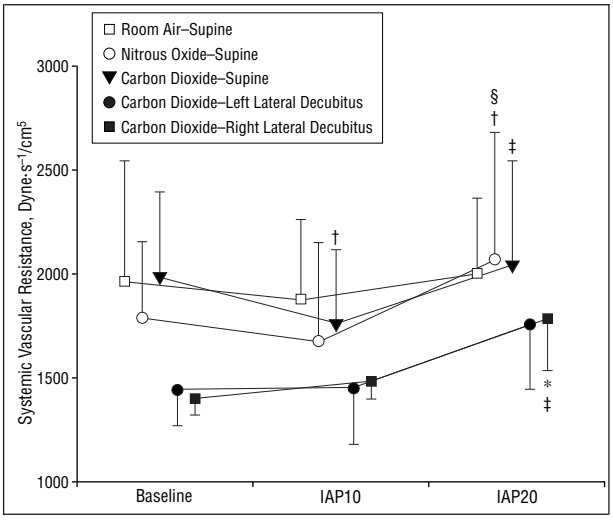

Figure 5. *Fluctuations in the systemic vascular resistance. At an intra-abdominal pressure of 20 mm Hg (IAP20), the systemic vascular resistance increased significantly in 3 groups. Asterisk indicates* P<*.01 vs baseline; dagger,* P<*.05 vs baseline; double dagger,* P<*.01 vs an intra-abdominal pressure of 10 mm Hg (IAP10); and section mark,* P<*.05 vs IAP10.*

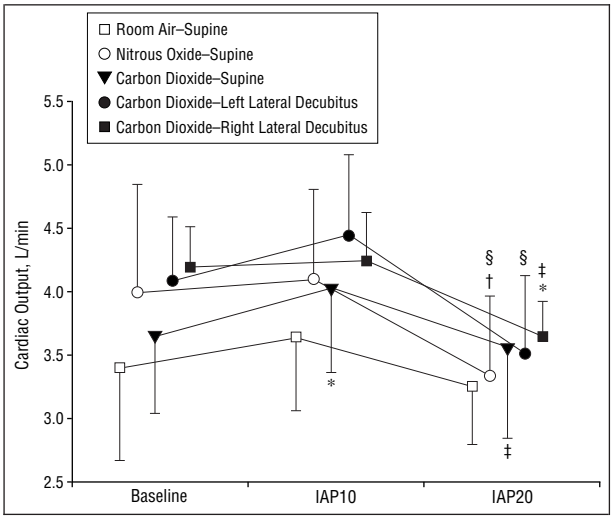

Figure 4. *Fluctuations in the cardiac output. At an intra-abdominal pressure of 20 mm Hg (IAP20), the cardiac output decreased significantly in 4 groups. Asterisk indicates* P<*.01 vs baseline; dagger,* P<*.05 vs baseline; double dagger,* P<*.01 vs intra-abdominal pressure of 10 mm Hg (IAP10); and section mark,* P<*.05 vs IAP10.*

amine, used for the induction of anesthesia, has been reported to increase the concentration of norepinephrine.[15] However, there were no significant differences in the baseline concentrations of catecholamines between any of the groups in our study.

Pneumoperitoneum can also affect hemodynamics. In animal studies, the cardiac output decreases at an IAP higher than 40 mm Hg.[16-18] The effects of IAP (<40 mm Hg) on the cardiac output can be positive or negative; the magnitude of IAP can cause either an increase or a decrease in cardiac output.[16,19] In clinical studies, the cardiac output has been reported to be reduced at an IAP higher than 40 mm Hg.[20] At an IAP lower than 40 mm Hg, the results are controversial.[20-22] When the IAP is low, the capacitance vessels are compressed but not collapsed. In contrast, at higher pressures, the capacitance vessels are collapsed.[23] The blood flow in the inferior vena cava was also reduced when the IAP was elevated.[16,17] The blood flow velocity in the femoral vein was significantly reduced during laparoscopic surgery at 14 mm Hg of IAP, which can disturb the venous return and thus stagnate blood flow.[24]

We hypothesized that the capacitance vessels were compressed but not collapsed at IAP10 that resulted in a relative increase in the venous return. On the other hand, the capacitance vessels were collapsed at IAP20 that resulted in a decrease of the cardiac output and an increase in the systemic vascular resistance due to a reduction of the venous return. A reduction in the cardiac output may stimulate the sympathetic nervous system, and thus increase plasma catecholamine concentrations.

The $PaCO_2$ increased significantly after carbon dioxide insufflation, and did not increase in any of the groups receiving air or nitrous oxide as an insufflation gas. The $PaCO_2$ during the pneumoperitoneum in the carbon dioxide groups was always less than 45 mm Hg. There were no significant differences in the plasma catecholamine concentrations between any of the groups at the baseline, IAP10, or IAP20. We therefore considered that the increase in $PaCO_2$ did not influence the catecholamine concentrations in our study.

In conclusion, the increase in the plasma catecholamine concentration was associated with an increase in IAP. Changes in venous return during insufflation may be responsible for this phenomenon. During laparoscopic surgery, the IAP should not be increased excessively, particularly in patients with hypertension, pheochromocytoma, or ischemic heart disease.

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Invited Commentary

The basis for the current investigation is a previous clinical study by the same authors in which they observed a rise in plasma catecholamine concentrations after the establishment of pneumoperitoneum at 15 mm Hg.[1] The authors are to be commended for their efforts to better characterize this phenomenon using an animal model, but the experimental design ultimately limits the usefulness of the conclusions. The short time spent at each pressure gives little time for equilibration, and the technique of stepping up from 10 mm Hg to 20 mm Hg after a 5-minute interval does not simulate clinical practice. The authors neglect to mention the very fine work of Ho and colleagues,[2] also in a porcine model, which demonstrated significant transperitoneal carbon dioxide absorption, with associated increases in systemic and pulmonary vascular resistance, when measured over 1 hour's time at 15 mm Hg. We are left to wonder why Mikami et al did not include measurements at 15 mm Hg, because this is the commonly used upper limit in the clinical setting (and the pressure at which their original clinical observations were made). The experiments resulted in a number of statistically significant differences, but are they clinically relevant? For example, in the subset most similar to the clinical scenario, the supine group undergoing carbon dioxide pneumoperitoneum, there is no significant difference in mean arterial pressure when comparing the baseline group with the group with an intra-abdominal pressure of 20 mm Hg. There is also no significant change in cardiac output or systemic vascular resistance when the baseline group and the group with an intra-abdominal pressure of 20 mm Hg are compared. This study provides an interesting insight into the acute catecholamine response to increases in abdominal compartment pressure. However, it has left some fundamental questions unanswered about the clinical importance of this phenomenon.

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