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Lack of neurohumoral response to pneumoperitoneum for laparoscopic cholecystectomy

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Abstract
Background: Pneumoperitoneum (PP) for laparoscopic surgery induces prompt changes in circulatory parameters. The rapid onset of these changes suggests a reflex origin, and the present study was undertaken to evaluate whether release of vasopressor substances could be responsible for these alterations. The influence of two different anesthesia techniques was also evaluated.
Methods: American Society of Anesthesiologists (ASA) class I patients, scheduled for laparoscopic cholecystectomy, were investigated. The first group ($n = 10$) was anesthetized intravenously. The second group ($n = 6$) had inhalation anesthesia. Plasma vasopressin, catecholamines, and plasma renin activity were investigated as neurohumoral vasopressor markers of circulatory stress. The general stress response to surgery was assessed by analysis of plasma cortisol.
Results: Induction of pneumoperitoneum caused no apparent activation of vasopressor substances, although several hemodynamic parameters responded promptly.
Conclusion: The hemodynamic alterations, seen at the establishment of PP during stable anesthesia, cannot be explained by elevation of vasopressor substances in circulating blood.

Key words: Intravenous anesthesia — Isoflurane anesthesia — Catecholamines — Pneumoperitoneum — Renin — Laparoscopic surgery — Vasopressin

Surgical trauma activates a stress response comprising neurohumoral, immunologic and metabolic factors. It has previously been demonstrated that the magnitude of the stress response is proportional to the degree of trauma [3]. It also has been shown that the anesthetic technique is of importance for the extent of trauma response [14]. Concerning laparoscopic surgery, it has been believed generally that trauma responses should be less accented than with open surgery, but this has not been verified [16, 18, 27].

In a previous study of propofol-fentanyl anesthetized patients, we demonstrated that abdominal insufflation of carbon dioxide for laparoscopic cholecystectomy gives rise to an almost instantaneous increase in blood pressure and systemic vascular resistance as well as to an increase in myocardial filling pressures [22]. This also has been shown by others [13, 21]. The rapid circulatory response to increased intra-abdominal pressure (IAP) at abdominal carbon dioxide insufflation, or so-called pneumoperitoneum (PP), indicated it to be of reflex origin. It has been suggested that this could be due to neurohumoral factors such as vasopressin, renin, and catecholamines [12]. The important vasopressor response mechanisms to trauma are in fact induced by the sympathetic nervous system, the renin–angiotensin system, and vasopressin stimulation [33]. These systems are also highly interactive [31].

The aim of this study was to investigate whether hemodynamic changes on induction of pneumoperitoneum under stable propofol-fentanyl anesthesia could be attributed to the release of vasopressor substances. To elucidate the influence of various anesthetic techniques, the neurohumoral responses on induction of pneumoperitoneum were studied in an additional group of patients anesthetized with isoflurane-N_2O. Invasive hemodynamic measurements were performed only in the propofol-fentanyl group.

Materials and methods

Patients

Patients scheduled to undergo laparoscopic cholecystectomy for gallstone disease were investigated after their informed consent was obtained. First, a group of 10 patients who had intravenous (IV) anesthesia were investi-

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gated, including central hemodynamic monitoring (IV group). To investigate whether various anesthesia types influenced the neurohumoral response differently, a second study was performed in patients who had inhalational anesthesia (inhal group). These patients were not invasively studied. The IV group consisted of three males and seven females, with a mean age of 39 years (range, 18–53 years) and a mean body weight of 71 kg (range, 48–90 kg). The inhal group consisted of six females, with a mean age of 41 years (range, 20–64 years) and a mean body weight of 58 kg (range, 53–65 kg). All patients were without signs of cardiopulmonary disease (ASA group I) and without endocrine or metabolic disease. The protocol was approved by the Ethical Committee for Human Studies at the Karolinska Hospital.

Anesthesia and protocol

All patients were premedicated with cetobemidone 5–10 mg.

The intravenous anesthesia group (IV group). After the IV administration of 0.2 mg of glycopyrrolate, the anesthesia was induced with propofol 2–3 mg/kg bodyweight (BW), fentanyl 1.5–2.5 μg/kg BW, and atracurium 0.5 mg/kg BW and maintained with propofol 4–8 mg × kg BW^{-1} × h^{-1}, fentanyl 1.5–3 μg × kg BW^{-1} × h^{-1}, and atracurium 0.2–0.4 mg × kg BW^{-1} × h^{-1}. The patients were mechanically ventilated with a mixture of oxygen and air having a fraction of inspired oxygen (FiO_2) of 0.35–0.40 by a ventilator (MCM 590, Dameca, Copenhagen, Denmark). After anesthesia induction, a radial arterial cannula (art. no. 4440-4, Viggo Spectramed, Swindon, UK) was inserted and used for mean arterial pressure (MAP) monitoring and for arterial blood sampling of catecholamines during surgery. A Swan-Ganz thermodilution catheter (AH-05050-H, Arrow Int. Inc., Reading, Pennsylvania, USA) was introduced by pressure tracing. At blood sampling times, MAP, central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) were recorded by a Hellige pressure recording device (cat. no. 120 214 29, Hellige GMBH, Freiburg, Germany), and cardiac output (CO) was determined by a Hewlett-Packard cardiac output computer (model 9520 A, American Edwards Laboratories, Irvine, CA, USA) as the mean of triplicates of 10-ml saline injectates. The heart rate (HR), FiO_2, endtidal carbon dioxide concentration ($ETCO_2$), and percutaneous oxygen saturation (SpO_2) were recorded by a Datex Ultima monitoring device (type ULT-S-23-01, Datex Instrumentarium Corp., Copenhagen, Denmark). The $PaCO_2$ also was measured by means of repeated arterial blood gas samples throughout the procedure.

Venous blood samples for analysis of cortisol, adrenaline, noradrenaline, and vasopressin were collected on five occasions: (1) at approximately 6:45 a.m. with the patients resting in bed at the surgical ward before premedication, (2) 5 min after the termination of carbon dioxide insufflation at the intended IAP level (11–13 mmHg), (3) after 1 h of surgery with the patients in a 15–20° head-up tilt, (4) after 2 h of surgery in the same position, and (5) at the postoperative unit 30 min after extubation. Plasma renin activity (PRA) was determined at occasions 1–3 and 5. The arterial and pulmonary artery catheters were removed before the patients were awakened. Arterial samples for analysis of adrenaline and noradrenaline were therefore collected at occasions 2–4. Three patients required less than 2 h of surgery. Consequently, the results from seven patients were evaluated at occasion 4. The urine excretion of adrenaline and noradrenaline was measured during 24 h, beginning at 7:00 a.m. on the day of surgery.

The inhalational anesthesia group (inhal group). The patients were given glycopyrrolate as in the IV group. The anesthesia was then induced by sodium pentothal 5–7 mg/kg BW. Fentanyl 0.1 mg and atracurium 0.5 mg/kg BW were given before intubation of the trachea. The anesthesia was then maintained by isoflurane 1–1.5% in a mixture of O_2/N_2O 35–40% and 60–65%, respectively, and the patients were mechanically ventilated as in the IV group.

Venous blood samples for analysis of cortisol, adrenaline, and vasopressin were collected (1) at approximately 6:45 a.m. with the patients resting in bed at the surgical ward before premedication, (2) 5 min after the termination of carbon dioxide insufflation at the intended IAP level (11–13 mmHg), (3) after 1 h of surgery with the patients in a 15–20° head-up tilt, (4) at the postoperative unit approximately 30 min after extubation. Noradrenaline and PRA also were measured after induction of anesthesia. Systolic blood pressure (SAP) was determined by a sphygmomanometer in conjunction with the blood sampling occasions. As in the IV group, HR, FiO_2, $ETCO_2$ and SpO_2 were recorded. No measurements were made at 2 h of surgery due to shorter operating time in this group.

In both groups, owing to resorption of carbon dioxide during the laparoscopic procedure, repeated adjustments of the minute ventilation were made to keep $ETCO_2$ within normal limits. During the investigation, a crystalloid solution was given at a rate of 2 ml × kg^{-1} × h^{-1} (Rehydrex® with Glucose 25 mg/ml, Kabi-Pharmacia, Sweden).

Surgery

Cholecystectomy was performed using four trocars: two 10-mm trocars placed midline and two 5-mm trocars placed laterally (Surgiport 171028 and 171016, respectively, Autosuture, U.S. Surgical Corp., Norwalk, Connecticut, USA). Carbon dioxide (AGA Gas Corp., Stockholm, Sweden) was insufflated into the peritoneal cavity by an electronic laparoflator (model no. 3500, Wiest, Unterhaching, Germany). The surgical field was visualized by a cold-light fountain (type 450 BV, Karl Storz Endoskope, Tuttlingen, Germany), by a video camera (Storz Autoexposure Camera, model no. 9050 PB, Karl Storz Endoskope, Tuttlingen, Germany), and by a color video monitor (model no. PVM-2043 MD, Sony, Japan). The cystic duct and artery were ligated using metal clips (Endoclip 176615, Autosuture, U.S. Surgical Corp., Norwalk, Connecticut, USA), and the gallbladder was dissected from bottom to top using diathermia. The IAP was continuously monitored and kept at a level of 11–13 mmHg. The postoperative course was without complications, and all patients were discharged within 3 postoperative days.

Sampling and analysis

At each sampling time approximately 20 ml of blood was collected. Samples were collected in heparinized tubes (143 U/10 ml) for determination of cortisol, catecholamines, and vasopressin, and in tubes primed with EDTA (K3 15% 0.054 ml, 0.34 M/10 ml) for measurement of plasma renin activity. Samples were immediately placed on ice, centrifuged for 10 min at 4°C, 3,000 rpm, and the aliquots were stored at −20° until batch analysis. Cortisol, vasopressin, and plasma renin activity were analyzed using commercial radioimmunoassay kits (Wallac Oy, Turku, Finland; Euro-Diagnostics BV, Malmö, Sweden; and Du Pont Company, Billerica, Mass., USA, respectively). Catecholamines were determined using HPLC and electrochemical detection [8]. The intra-assay coefficients of variation were 0.04 for noradrenaline and 0.06 for adrenaline.

Statistics

Data are presented as means ± *SD*. Statistical analysis was performed by nonparametric analysis of variance (Friedmans test). Wilcoxon's rank sum test was used as post hoc test. Significant differences are given at the 5% level.

Results

In both patient groups, the blood pressure was significantly elevated during pneumoperitoneum and surgery compared with baseline values (Tables 1 and 2). After the establishment of pneumoperitoneum, MAP increased by 37 ± 25% ($p < 0.01$) in the IV group. The online registration of blood pressure available in this group showed an increase of the MAP already during the insufflation of carbon dioxide. In the inhal group, SAP was increased by 22 ± 15% ($p < 0.01$). Heart rate was not significantly affected (Tables 1 and 2). In the IV group (Table 1) the systemic vascular resistance (SVR) increased by 40 ± 36% ($p < 0.01$) at the establishment of pneumoperitoneum, and CVP and PCWP were increased by 65 ± 48% ($p < 0.01$) and 32 ± 29% ($p < 0.01$),

Table 1. Hormones and hemodynamic data from the intravenous group[a]

		Awake	Anesth	PP	1h PP	2h PP	Postop
Vasopressin	(pmol/l)	1.6 ± 0.7	—	2.2 ± 1.6[b]	21.5 ± 19.0[b]	45.6 ± 39.0[b]	4.7 ± 3.3[b]
PRA	(ng/ml × h)	3.0 ± 3.2	—	6.6 ± 12.2	6.7 ± 7.9[b]	—	2.8 ± 4.7
V-noradrenaline	(nmol/l)	1.4 ± 0.6	—	0.6 ± 0.3[b]	1.0 ± 0.5	1.1 ± 0.7	2.8 ± 3.5
V-adrenaline	(nmol/l)	0.2 ± 0.1	—	0.2 ± 0.1	0.2 ± 0.2	0.2 ± 0.2	0.2 ± 0.1
A-noradrenaline	(nmol/l)	—	—	0.6 ± 0.4	1.1 ± 0.8	1.0 ± 1.0	—
A-adrenaline	(nmol/l)	—	—	0.1 ± 0.0	0.2 ± 0.1	0.4 ± 0.3[b]	—
Cortisol	(nmol/l)	455 ± 144	—	84 ± 43[b]	249 ± 179[b]	502 ± 242	458 ± 224
HR	(beats/min)	81 ± 10	76 ± 11	62 ± 8	71 ± 12	69 ± 14	70 ± 9
MAP	(mmHg)	87 ± 8	63 ± 8	86 ± 10[b]	90 ± 15[b]	84 ± 17[b]	—
SVR	(units)	—	1392 ± 520	1854 ± 471[b]	1981 ± 461[b]	1753 ± 421	—
CVP	(mmHg)	—	7 ± 3	11 ± 3[b]	6 ± 3	7 ± 2	—
PCWP	(mmHg)	—	11 ± 3	14 ± 3[b]	10 ± 5	10 ± 4	—

[a]Data from 10 patients anesthetized by propofol-fentanyl prior to and after establishment of pneumoperitoneum for laparoscopic cholecystectomy
[b]Level significantly different from that in the awake state ($p < 0.05$)
MAP = mean arterial pressure, SVR = systemic vascular resistance, CVP = central venous pressure, PCWP = pulmonary capillary wedge pressure

Table 2. Hormones and hemodynamic data from the inhalation anesthesia group[a]

		Awake	Anesth	PP	1h PP	Postop
Vasopressin	(pmol/l)	1.4 ± 0.6	—	1.1 ± 0.1	5.4 ± 10.6	35.6 ± 31.5[b]
PRA	(ng/mL × h)	1.5 ± 0.8	4.9 ± 3.6[b]	7.6 ± 2.9[b,c]	12.4 ± 5.6[b,c]	5.3 ± 3.1[b]
V-noradrenaline	(nmol/l)	1.4 ± 0.7	0.6 ± 0.2	1.4 ± 0.5[c]	1.4 ± 0.6[c]	2.6 ± 1.8[c]
V-adrenaline	(nmol/l)	0.2 ± 0.1	0.2 ± 0.1	0.3 ± 0.2	0.4 ± 0.2[b,c]	1.0 ± 0.6[b,c]
Cortisol	(nmol/l)	509 ± 164	206 ± 92[b]	172 ± 65[b,c]	230 ± 195[b]	680 ± 183[c]
HR	(beats/min)	81 ± 10	75 ± 5	77 ± 4	78 ± 10	77 ± 17
SAP	(mmHg)	127 ± 13	90 ± 5	105 ± 6[b]	102 ± 7[b]	113 ± 15[b]

[a]Data from six patients undergoing inhalation anesthesia prior to and after establishment of pneumoperitoneum for laparoscopic cholecystectomy
[b]Level is significantly different from that in the awake state ($p < 0.05$)
[c]Level is significantly different from that during anesthesia ($p < 0.05$)
SAP = systolic arterial pressure

respectively (Table 1). CO was 3.5 ± 0.9 l/min during stable anesthesia and was not significantly affected throughout the investigation (data not shown). The average operating time was 114 min (range, 60–165 min) in the IV group and 75 min (range, 60–115 min) in the inhal group.

Plasma catecholamines

In both the IV and inhal groups the levels of adrenaline and noradrenaline were generally low (Figs. 1 and 2, see Tables 1 and 2). In the IV group, noradrenaline levels were decreased after pneumoperitoneum induction compared with those in the awake state. Otherwise, noradrenaline was unaffected. In the inhal group after the induction of pneumoperitoneum, noradrenaline level was unaffected compared with that in the awake state, whereas compared with noradrenaline level in the anesthetized state, small but significant elevations of noradrenaline occurred after induction of pneumoperitoneum (from 0.6 ± 0.2 to 1.4 ± 0.5 nmol/l), at 1 h of pneumoperitoneum, and postoperatively ($p < 0.05$). Adrenaline levels were not affected by pneumoperitoneum establishment in either group (see Tables 1 and 2). At 1 h of pneumoperitoneum and postoperatively, adrenaline level was elevated compared with that in the awake state and the anesthetized state in the inhal group ($p < 0.05$). Arterial levels of adrenaline and noradrenaline, which were analyzed during pneumoperitoneum and surgery in the IV group, were also low and unaffected with the exception of a small increase of adrenaline levels at 2 h of pneumoperitoneum (see Table 1).

Urine catecholamines

The excretion during 24 h of noradrenaline and adrenaline, which was measured in the IV group, was within the normal range for healthy controls pursuing normal daily activity: average 226 nmol for noradrenaline and 69 nmol for adrenaline.

Vasopressin

In the IV group, there was a small elevation of vasopressin at pneumoperitoneum establishment (from 1.57 ± 0.73 to 2.19 ± 1.55 pmol/l, $p < 0.05$) (see Table 1 and Fig. 1). During surgery, vasopressin levels rose successively, being markedly elevated, compared with the baseline level, at 1 h of surgery and at 2 h of surgery ($p < 0.01$). Postoperatively, the values were again diminished. In the inhal group, the vasopressin levels remained low and unaffected during surgery, but instead were markedly elevated postoperatively ($p < 0.05$) (see Table 2 and Fig. 2).

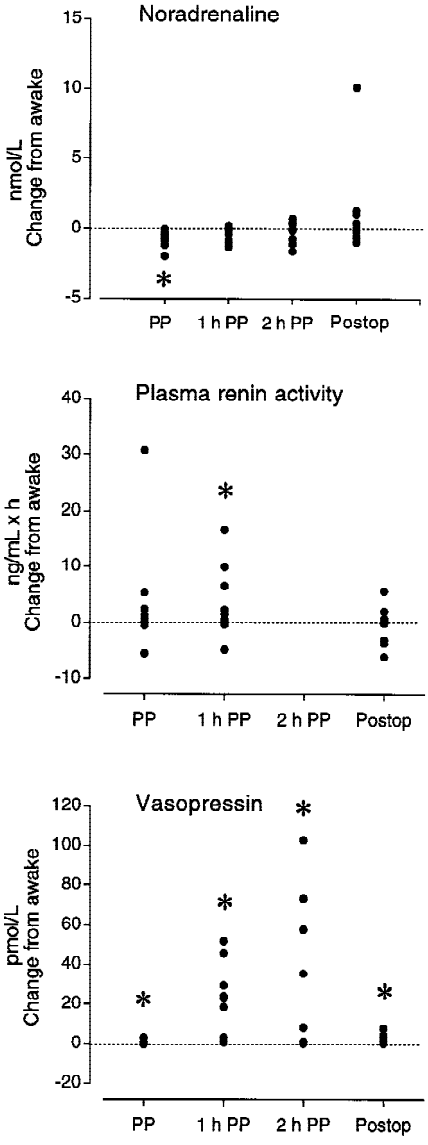

Fig. 1. Change from the awake state of venous plasma noradrenaline, renin activity, and vasopressin in 10 patients anesthetized by propofol-fentanyl, prior to and after establishment of pneumoperitoneum for laparoscopic cholecystectomy. *Level is significantly different from that in the awake state ($p < 0.05$).

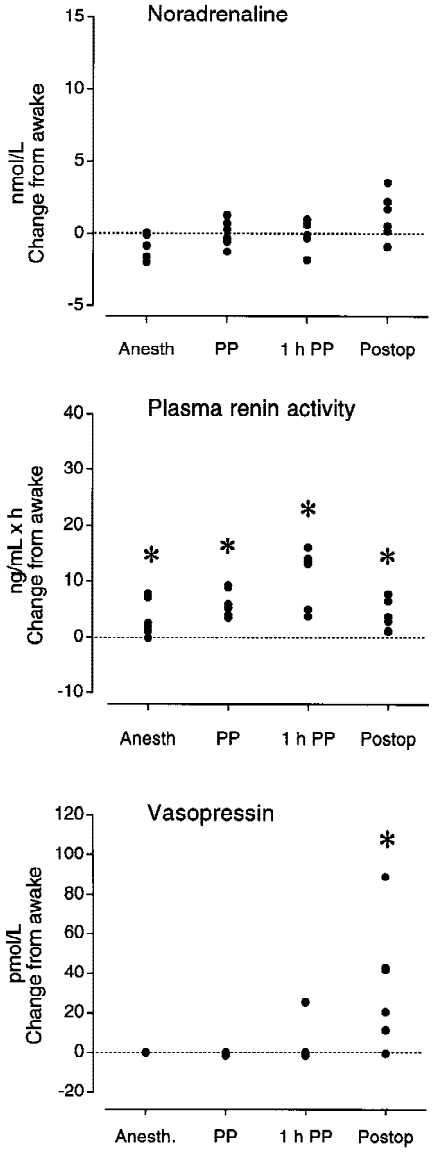

Fig. 2. Change from the awake state of venous plasma noradrenaline, renin activity, and vasopressin in six patients undergoing inhalation anesthesia, prior to and after establishment of pneumoperitoneum for laparoscopic cholecystectomy. *Level is significantly different from that in the awake state ($p < 0.05$).

Renin activity

In the IV group, PRA was not affected by pneumoperitoneum establishment, but was elevated at 1 h of surgery ($p < 0.05$) and postoperatively returned to the baseline level (see Table 1 and Fig. 1). In the inhal group, PRA levels rose successively during the procedure and were higher at all measurement occasions compared with those of the awake state ($p < 0.05$). After pneumoperitoneum induction and during surgery, there was also a minor but reproducible elevation compared with PRA levels of the anesthetized state ($p < 0.05$) (see Table 2 and Fig. 2).

Cortisol

In both groups, the preoperative early morning value was in the upper normal range, reflecting the natural diurnal rhythm of this hormone [12]. During anesthesia and surgery, there was a decrease in cortisol during the first hour of pneumoperitoneum. Postoperatively, the values returned to the preoperative level (see Tables 1 and 2).

Discussion

This study gives no evident support for the hypothesis that the prompt circulatory effects at the induction of pneumoperitoneum are caused by vasopressors. Although the minute elevations of vasopressin in the IV group and of PRA in the inhal group were statistically significant, they were so minor that they could not exert the hemodynamic effects seen at pneumoperitoneum induction. Furthermore, stress hormone response to the surgical trauma, assessed as cortisol and catecholamines, was blunted, as indicated by

low values during surgery. The patterns of cortisol and catecholamine reaction were in accordance with previous findings in which adequate anesthesia provided a good blockade against surgical stress, that is, an attenuation of the stress hormone response during anesthesia with a gradual activation during surgery as well as postoperatively [3, 30].

Nevertheless, hemodynamically, there were signs of an elevated left ventricular preload as well as afterload following the induction of pneumoperitoneum. In the IV group, CVP and PCWP as well as MAP and SVR were increased. Also, in the inhal group, the finding of an increased blood pressure was reproduced. The three relevant vasopressors studied are discussed separately as follows.

Vasopressin

Vasopressin is released mainly in response to increases in plasma osmolality and to systemic hypotension. Vasopressin is also released in response to a number of other factors, among which are positive pressure breathing, postural changes, nausea, hypoxia, hypercapnia, acidosis, and drug administration. Whereas surgical stress is a potent stimulus for vasopressin release [20, 24], it has been found that stable anesthesia of different kinds, including various inhalational anesthesia regimens and fentanyl anesthesia, do not induce vasopressin secretion [24]. This finding was reproduced in the present study using propofol-fentanyl and isoflurane anesthesia. In humans, vasopressin has been shown to produce vasoconstriction in skin and skeletal muscle at low concentrations: 3.4 pg/ml (i.e., approximately 3.4 pmol/l [9]. Levels exceeding 30 pg/ml (i.e., approximately 30 pmol/l), however, are required to exert pressor activity in conscious rats, dogs, and humans [1]. Furthermore, in dogs, vasopressin is found to be a potent systemic vasoconstrictor during hemorrhage [2]. The circulating plasma level in anesthetized humans, where effects on systemic blood pressure is observed, is not known.

Vasopressin also has been shown to increase in response to increased IAP, both in animals [17] and in humans [19]. In the human study, an IAP level of 45 mmHg resulted in a 45-fold increase in vasopressin levels compared with values before pneumoperitoneum. In these studies, the IAP level has been so high that venous return has been impaired. It has been documented in dogs that high levels of IAP cause a reduction of venous return measured as an increased femoral vein pressure [11] and as a reduced inferior vena caval flow, causing a reduced cardiac output [11, 28]. These findings were reported beginning at an IAP level of 10 mmHg and higher [28] and of 20 mmHg and higher [11]. An important mechanism behind the vasopressin release in these studies is probably the reduced filling of the central circulation that mimics the situation after hemorrhage. Vasopressin is then released in response to a change in input from cardiovascular stretch receptors. Thus, in situations with high IAP levels, the increased vasopressin release seen is probably a response to circulatory alterations.

In the present study using clinical pneumoperitoneum (11–13 mmHg), there was no clinically relevant vasopressin increase at pneumoperitoneum establishment, neither in the IV group (1.6 ± 0.7 to 2.2 ± 1.6) nor in the inhal group. The late elevation of vasopressin levels could also be a reflection of the general vasopressin response to surgery because the time course for its activation in this study parallels that otherwise seen during general surgery [3, 7]. It has also been proposed that peritoneal stretch or pressure receptors could mediate vasopressin-releasing stimuli [25], and an activation of vasopressin in conjunction with visceral traction has been observed [20].

Catecholamines

In the present study, catecholamine levels were low and well within the normal range throughout the investigation. In the IV group, noradrenaline was even lower after pneumoperitoneum establishment compared with the baseline level. In the inhal group, the noradrenaline level was the same after pneumoperitoneum induction as at baseline. The urine content of catecholamines over a 24-h period was not elevated. Although these findings suggest essentially normal levels of sympathetic activity, the fact can not be ruled out, however, that the catecholamines are involved in hemodynamic effects during the induction of pneumoperitoneum. The immediate onset of the circulatory changes suggests a rapid reflex activation, and sympathetic activation is the most rapid mediator of circulatory changes known [6]. There are difficulties, however, in adequately assessing regional catecholamine activation when blood is collected systemically. The activity within the sympathetic nervous system is highly differentiated [10], and the release of noradrenaline from different organs in the body shows a substantial variation [4, 5]. It may be that the increased SVR after pneumoperitoneum induction is due to a differentiated increase in sympathetic nerve activity goes to resistance vasculatures and is not a response to resistance vasculatures such as in skeletal muscle, because of afferent stimulation from the spanchnic region not detectable in systemic venous or arterial blood samples.

Renin-angiotensin system

Although there was an elevation of PRA in the inhal group (less than 3 ng/ml × h), also after pneumoperitoneum establishment, these levels are still low and not considered to exert circulatory effects [28]. The renin–angiotensin system is most effectively activated by lowered renal perfusion pressure due to hypotension [15]. The current blood pressure level did not cause activation of the renin–angiotensin system with high levels of PRA during anesthesia. It is further evident that the present pressor response during pneumoperitoneum did not activate the renin–angiotensin system directly, or secondarily as a result of sympathetic activation.

In the literature, there is controversy concerning the neurohumoral response to pneumoperitoneum. It was suggested in a previous study that the elevated MAP and SVR during pneumoperitoneum would be caused by an increase in vasopressin release [12]. In that study, there was a rapid increase of vasopressin at the establishment of pneumoperitoneum. However, at the onset of CO_2 insufflation, the anesthetic depth had to be augmented immediately [12, personal communication], and during the procedure isoflurane was administered ‘‘as needed.’’ It may be that a low

anesthetic level during painful CO_2 administration caused the marked vasopressin release during pneumoperitoneum induction. Moreover, compared with values before pneumoperitoneum, the same study also reported increased levels of adrenaline and noradrenaline 5 minutes after the establishment of pneumoperitoneum (from 36 to 181 ng/l and from 222 to 408 ng/l, respectively), which further support this assumption, as also does the detection of an increased level of plasma cortisol already after 15 min of pneumoperitoneum (from 53 μg/l before pneumoperitoneum to 175 μg/l) [12]. It has also been suggested that a renin–angiotensin activation could be responsible for the pressor response on induction of pneumoperitoneum [23]. However, at the onset of hemodynamic response, plasma renin was unaffected, ruling out a direct causal relationship. Lefebvre et al. [16] in gynecological laparoscopic surgery using halothane anesthesia reported no increase in adrenaline and noradrenaline levels in blood samples collected at the end of carbon dioxide insufflation. Mealy et al. [18] found an increase in urinary vanillylmandelic acid in a laparoscopic cholecystectomy group, which however does not reflect the acute response to pneumoperitoneum.

In the absence of apparent vasopressor activation, it can be speculated that the increased IAP causes a redistribution of pooled splanchnic blood to the systemic circulation, which results in an autotransfusion. This in turn may contribute to increased filling pressures. In a canine open-chest model, Takata et al. [32] showed that an increased IAP increases venous return measured in the inferior vena cava at the level of the diaphragm, as long as the IAP level does not exceed the pressure in the inferior vena cava. Another finding indicating a redistribution of the blood volume is that after the establishment of pneumoperitoneum, despite positioning of the patient in a head-up tilt, the filling pressures were not reduced compared with those of the horizontal position without pneumoperitoneum. On the basis of the present hemodynamic measurements, it is considered that the patients were essentially normovolemic, and therefore that the results of this investigation apply to the situation with normal circulation. In hyper- and hypovolemic patients, hemodynamics, and possibly neurohumoral response, could be different.

In conclusion, in the present study, irrespective of anesthesia technique, a neurohumoral origin of the circulatory alterations seen immediately after the establishment of pneumoperitoneum was not detected. According to the present data the possibility cannot be excluded that a differentiated sympathetic reflex response may play a hemodynamically significant role at the establishment of pneumoperitoneum, but other mechanisms need to be investigated further.

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