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Hemodynamic Changes Induced by Laparoscopy and Their Endocrine Correlates: Effects of Clonidine

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Objectives. **We investigated endocrine correlates of the hemodynamic changes induced by carbon dioxide pneumoperitoneum (PNO). We then studied whether clonidine might modulate the hemodynamic changes induced by PNO by reducing release of catecholamines and vasopressin.**

Background. **Both mechanical and neurohumoral factors contribute to the hemodynamic changes induced by carbon dioxide PNO. Several mediators have been proposed, but no study has correlated hemodynamic changes with changes in levels of these potential mediators.**

Methods. **We conducted two studies, each including 20 healthy patients scheduled for elective laparoscopic cholecystectomy. In the first study serial measurements of hemodynamics (thermodilution technique) were done during laparoscopy and after exsufflation. Plasma concentrations of cortisol, catecholamines, vasopressin, renin, endothelin and prostaglandins were measured at the same time points. In the second study patients were randomly allocated to receive 8 μg/kg clonidine infused over 1 h or placebo before PNO. Hemodynamics and plasma levels of cortisol, catecholamines and vasopressin were measured during PNO and after exsufflation.**

Results. **Peritoneal insufflation resulted in a significant reduction of cardiac output (18 ± 4%) and increases in mean arterial pressure (39 ± 8%) and systemic (70 ± 12%) and pulmonary (98 ± 18%) vascular resistances. Laparoscopy resulted in progressive and significant increases in plasma concentrations of cortisol, epinephrine, norepinephrine and renin. Vasopressin plasma concentrations markedly increased immediately after the beginning of PNO (before PNO 6 ± 4 pg/ml; during PNO 129 ± 42 pg/ml; $p < 0.05$). The profile of vasopressin release paralleled the time course of changes in systemic vascular resistance. Prostaglandins and endothelin did not change significantly. Clonidine significantly reduced mean arterial pressure, heart rate and the increase in systemic vascular resistance. Clonidine also significantly reduced catecholamine concentrations but did not alter vasopressin and cortisol plasma concentrations.**

Conclusions. **Vasopressin and catecholamines probably mediate the increase in systemic vascular resistance observed during PNO. Clonidine before PNO reduces catecholamine release and attenuates hemodynamic changes during laparoscopy.**

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The multiple benefits reported after laparoscopy explain its increasing use (1). Consequently, laparoscopy has now become the standard technique for cholecystectomy. However, the pneumoperitoneum (PNO) required for laparoscopy results in pathophysiologic changes (1). More particularly, changes in cardiovascular function occur during laparoscopy. These are characterized by an increase in arterial pressure and systemic and pulmonary vascular resistances (SVR and PVR) early after the beginning of intraabdominal insufflation, with no significant changes in heart rate (HR). A 10% to 30% decrease in cardiac output has also been reported in most studies (1–3).

Both mechanical and neurohumoral factors contribute to these hemodynamic changes (2,4). Several mediators have been proposed: catecholamines (5,6), prostaglandins (7), renin (8) and vasopressin (9–11). Unfortunately, no study has correlated hemodynamic changes with changes in levels of these potential mediators. Therefore, we first investigated endocrine correlates of the hemodynamic changes induced by PNO during laparoscopic cholecystectomy in healthy patients. Interestingly, alpha$_2$-adrenergic agonists have been shown to improve hemodynamic stability during gynecologic laparoscopy (12,13). Moreover, clonidine inhibits the release of catecholamines (14) and also blocks the release of vasopressin in dogs (15). We therefore tested the hypothesis that clonidine might attenuate the hemodynamic changes induced by PNO by reducing release of these substances.

Methods

Two studies were conducted after our institution's Ethics Committee gave approval and after patients gave their informed consent. Patients in each study were scheduled for

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Abbreviations and Acronyms

ASA = American Society of Anesthesiologists
HR = heart rate
MAP = mean arterial pressure
PCO_2 = partial pressure of carbon dioxide
PCWP = pulmonary capillary wedge pressure
PGE_2 = prostaglandin E_2
PNO = pneumoperitoneum
PVR = pulmonary vascular resistance
RAP = right atrial pressure
$S\bar{v}O_2$ = mixed venous blood oxygen saturation
SVR = systemic vascular resistance

elective laparoscopic cholecystectomy. Inclusion criteria were body weight no more than 20% above ideal weight, age between 18 and 70 years, absence of acute cholecystitis and no cardiorespiratory disease or medications. We used the same anesthetic technique in both studies. All patients were given 50 mg hydroxyzine orally 2 h before surgery and an intramuscular injection of 5 mg midazolam and 0.25 mg atropine before transfer to surgery. General anesthesia was induced with 15 μg sufentanil and 5 mg/kg thiopental. After orotracheal intubation facilitated with 0.5 mg/kg atracurium, anesthesia was maintained with 50% nitrous oxide in oxygen and isoflurane. Isoflurane concentrations were adapted to maintain hemodynamic stability by an experienced anesthesiologist; mean arterial pressure (MAP) was not allowed to increase more than 20% above preinduction value. In addition to clinical signs, the anesthesiologist used routine monitoring for laparoscopic cholecystectomy (i.e., automated oscillometric arterial blood pressure, electrocardiogram, capnography and pulse oximetry), but was unaware of the information derived from the invasive monitoring described below as well as of the arterial blood gas analyses. During surgery minute ventilation was controlled (Servo 900C; Siemens Elema, Stockholm, Sweden) and adjusted to keep the expired end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$) between 30 and 40 mm Hg. Respiratory rate was kept constant at 10-min. During laparoscopy intraabdominal pressure was automatically maintained at 14 mm Hg by a carbon dioxide insufflator (Richard Wolf; Knittlingen, Germany).

Study 1: Hemodynamic Data and Endocrine Correlates. Twenty American Society of Anesthesiologists (ASA) patients in physical status 1 and 2 were included in this study. Fasting and intraoperative fluid losses were compensated by a continuous intravenous infusion (5 $ml \cdot kg^{-1} \cdot h^{-1}$) of lactated Ringer's solution.

Hemodynamic and metabolic parameters. A radial artery was cannulated and a 7.5F thermodilution pulmonary artery catheter was introduced via the right internal jugular vein before induction of anesthesia. The following parameters were recorded on a Datex AS/3 monitor (Datex-Engström, Helsinki, Finland): MAP, right atrial pressure (RAP), pulmonary artery pressure and pulmonary capillary wedge pressure (PCWP) as well as HR. Cardiac output was measured by the Datex AS/3 monitor using the average of three measurements made at the end of expiration. Systemic vascular resistance and PVR were automatically computed by the Datex AS/3 monitor. Data were collected before the induction of anesthesia; 10 min after the induction of anesthesia; 10 min after tilting into a 10° head-up position; 5, 15 and 30 min after the beginning of insufflation; and finally 30 min after exsufflation. At this last time point anesthesia had been terminated for approximately 15 min and the patients, extubated, were breathing spontaneously in the horizontal position. The pressure transducer was located at the level of the right atrium and was moved after tilting to remain at this level. At the same time points arterial and mixed venous blood samples were drawn for blood gas analysis (288 Blood Gas System; Ciba Corning Diagnostics Corp., Medfield, Massachusetts). Oxygen transport and oxygen consumption were calculated according to standard formulas. Plasma lactate concentrations were also measured (Socolab, Limal, Belgium).

Endocrine parameters. Arterial blood samples were collected at the same time points as above for assay of the following hormones: cortisol (Radim, Liège, Belgium); catecholamines (16); renin (ERIA Diagnostics Pasteur, Marne la Coquette, France); endothelin (Amersham International, Amersham, United Kingdom); vasopressin (Bühlmann Laboratories AG, Basel, Switzerland); vasopressin–neurophysin (17); and prostaglandin E_2 (PGE_2), 6-keto-$PGF_{1\alpha}$ (a metabolite of prostacyclin) and TxB_2 (a metabolite of thromboxane) (Cayman Chemical, Ann Arbor, Michigan). Cortisol was used as an index of intraoperative stress; the other hormones were selected for their known vasoactive properties. Vasopressin–neurophysin, released concomitantly with vasopressin, is more stable in the blood than the active nonapeptide. The assay of the inactive peptide was used to validate measured plasma concentrations of vasopressin.

Study 2: Effects of Clonidine on Hemodynamic and Endocrine Changes. After the induction of anesthesia, 20 ASA physical status 1 and 2 patients were randomly allocated to receive either 8 $\mu g \cdot kg^{-1}$ clonidine intravenously over 1 h or the same volume of saline placebo in a double-blind fashion. This dose of clonidine was selected to approach doses reported to inhibit vasopressin release in animal studies (15). To avoid potential severe hypotension as a result of clonidine treatment, all patients received 500 ml lactated Ringer's solution before the induction of anesthesia and peritoneal insufflation was initiated with the patient in the horizontal position. Intraoperatively, the intravenous infusion of lactated Ringer's solution was 5 $ml \cdot kg^{-1} \cdot h^{-1}$. Because invasive monitoring was performed after the induction of anesthesia to avoid patient discomfort, preoperative cardiac function was assessed, using transthoracic echocardiography, on the day before surgery by the same investigator (J.L.C.), who was unaware of the patient allocation group.

Hemodynamic and metabolic parameters. The same hemodynamic parameters as in the first part of the study were recorded. Data were collected at the end of the infusion of clonidine or placebo and before induction of the PNO, 5 min after the beginning of peritoneal insufflation with the patient in supine position, 15 and 30 min after the beginning of insuffla-

Table 1. Hemodynamic Changes During Laparoscopy (Study 1)

	Before Induction	After Induction	Head Up	Pneumoperitoneum 5 min	Pneumoperitoneum 15 min	Pneumoperitoneum 30 min	After Surgery
MAP (mm Hg)	97 ± 3	90 ± 3	74 ± 3*	102 ± 4†	104 ± 4†	93 ± 4†	107 ± 4†
HR (beats·min^{-1})	77 ± 3	83 ± 3	77 ± 3	83 ± 4	84 ± 3	84 ± 4	80 ± 4
RAP (mm Hg)	8 ± 1	9 ± 1	6 ± 1*	11 ± 1†	11 ± 1†	10 ± 2†	8 ± 1
PCWP (mm Hg)	10 ± 1	9 ± 1	7 ± 1*	14 ± 1*†	15 ± 1*†	13 ± 1*†	10 ± 1
CO (L·min^{-1})	6.0 ± 0.3	4.6 ± 0.3*	3.6 ± 0.2*	3.1 ± 0.2*†	4.2 ± 0.2*	3.9 ± 0.3*	5.9 ± 0.4
SVR (dyn·s·cm^{-5})	1,218 ± 56	1,504 ± 98	1,561 ± 89	2,500 ± 198*†	1,836 ± 112*†	1,805 ± 97*	1,398 ± 72
PVR (dyn·s·cm^{-5})	250 ± 23	311 ± 29	302 ± 28	540 ± 50*†	444 ± 30*†	330 ± 36*†	292 ± 25
Isoflurane (%)	—	0.40 ± 0.03	0.36 ± 0.03	0.78 ± 0.05†	1.00 ± 0.06†	0.91 ± 0.07†	—

Hemodynamic changes during laparoscopic cholecystectomy and end-tidal isoflurane concentrations: mean arterial pressure (MAP), heart rate (HR), right atrial pressure (RAP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO), systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were measured or calculated before the induction of anesthesia; 10 min after the induction of anesthesia; 10 min after tilting into a 10° head-up position; 5, 15 and 30 min after the beginning of insufflation; and 30 min after exsufflation. Results are mean ± SEM. *$p < 0.05$ compared with before induction; †$p < 0.05$ compared with head-up tilt.

tion with the patient tilted to a 10° head-up position, 5 min after exsufflation with the patient still tilted to a 10° head-up position, and finally 30 min after exsufflation, approximately 15 min after the end of anesthesia and tracheal extubation with the patient in horizontal position breathing spontaneously. Mixed venous blood oxygen saturation ($S\bar{v}O_2$) was also measured at the same time points.

Endocrine parameters. Arterial blood samples were collected at the same time points to assay plasma cortisol, catecholamine and vasopressin concentrations. Plasma clonidine concentrations were also assayed 5 min after the beginning of peritoneal insufflation with the patient in supine position using a radioimmunoassay. The sensitivity was 0.1 ng/ml with a coefficient of variation of <15%.

Statistical analysis. Results are reported as mean ± SEM. Data were analyzed by one-way analysis of variance for repeated measures followed by Scheffé's test for multiple comparisons (study 1). Because distributions were not normal at some time points (from 5 min after the beginning of peritoneal insufflation until approximately 15 min after the end of anesthesia extubation) for epinephrine, norepinephrine and vasopressin, analysis was applied after logarithmic transformation. In the second study demographic data were compared using the unpaired Student *t* test. To assess the effect of clonidine, data were analyzed by two-way analysis of variance for repeated measures followed by the Newman–Keuls' test. Results were considered to be statistically significant at the 5% critical level.

Results

Study 1. Morphometric characteristics of the patients were: age 46 ± 5 years, sex (F/M) 14/6, weight 67 ± 4 kg and height 164 ± 3 cm. The duration of PNO was 67 ± 7 min. After the induction of anesthesia cardiac output decreased (Table 1). Tilting the patient to a 10° head-up position resulted in a significant decrease in RAP and PCWP. Consequently, cardiac output and MAP further decreased. Peritoneal insufflation at 5 min resulted in a significant reduction (18 ± 4%) of cardiac output, and a rise of MAP (39 ± 8%). Right atrial pressure and PCWP were significantly increased during PNO. Systemic and pulmonary vascular resistances also increased after peritoneal insufflation (SVR 70 ± 12%, PVR 98 ± 18%). Concentrations of isoflurane were increased to correct the increases in MAP. Simultaneously, partial correction of cardiac output, SVR and PVR occurred. However, these variables remained significantly different from preoperative values during PNO. After exsufflation all hemodynamic parameters returned to preoperative values (Table 1).

Changes in oxygen delivery paralleled the changes of cardiac output. Oxygen consumption was significantly reduced during anesthesia and surgery, but was significantly increased 30 min after exsufflation. Intraoperatively $S\bar{v}O_2$ remained normal (>70%). After exsufflation $S\bar{v}O_2$ significantly decreased. Lactate plasma concentrations progressively and significantly increased during laparoscopy, but remained normal (<2.0 mmol/L) (Table 2).

Five minutes after the beginning of peritoneal insufflation, PNO rapidly resulted in a marked release of vasopressin and neurophysin. Plasma concentrations of vasopressin then decreased, whereas plasma concentrations of neurophysin plateaued (Fig. 1). The profile of vasopressin release closely resembled the time course of changes in SVR. Plasma concentrations of epinephrine, norepinephrine and renin also increased during laparoscopy, but these changes were more progressive than the increase in SVR. Plasma concentrations of cortisol gradually increased during surgery (15 and 30 min after the beginning of insufflation) and in the immediate postoperative period. Plasma concentrations of endothelin, TxB_2, 6-keto-$PGF_{1\alpha}$ and PGE_2 did not change significantly (Table 3).

Study 2. Morphometric characteristics of the patients, duration of PNO and preoperative hemodynamic data were similar in the placebo and the clonidine groups (Table 4). The infusion of clonidine resulted in a plasma concentration of clonidine of 4.3 ± 0.3 ng/ml at 5 min after the beginning of

Table 2. Metabolic Changes During Laparoscopy (Study 1)

	Before Induction	After Induction	Head Up	Pneumoperitoneum 5 min	Pneumoperitoneum 15 min	Pneumoperitoneum 30 min	After Surgery
$PaCO_2$ (mm Hg)	40.8 ± 0.7	37.5 ± 1.1*	34.4 ± 0.6*	35.9 ± 0.8*	39.4 ± 0.9	37.9 ± 0.8	42.8 ± 1.1†
PaO_2 (mm Hg)	87 ± 3	242 ± 11*	210 ± 14*	223 ± 12*	223 ± 12*	212 ± 12*	109 ± 13
DO_2 (ml·min^{-1}·m^{-2})	635 ± 20	523 ± 25*	407 ± 24*	337 ± 23*†	461 ± 26*	415 ± 26*	612 ± 37†
$\dot{V}O_2$ (ml·min^{-1}·m^{-2})	135 ± 9	104 ± 5*	105 ± 5*	89 ± 6*	89 ± 5*	94 ± 4*	193 ± 17*†
$S\bar{v}O_2$ (%)	75 ± 1	81 ± 1*	75 ± 1	74 ± 2	81 ± 1*	78 ± 1	67 ± 2*
Lactate mmol·L^{-1}	0.80 ± 0.05	0.84 ± 0.08	0.96 ± 0.07	1.21 ± 0.08*	1.44 ± 0.09*	1.4 ± 0.09*	1.57 ± 0.15*

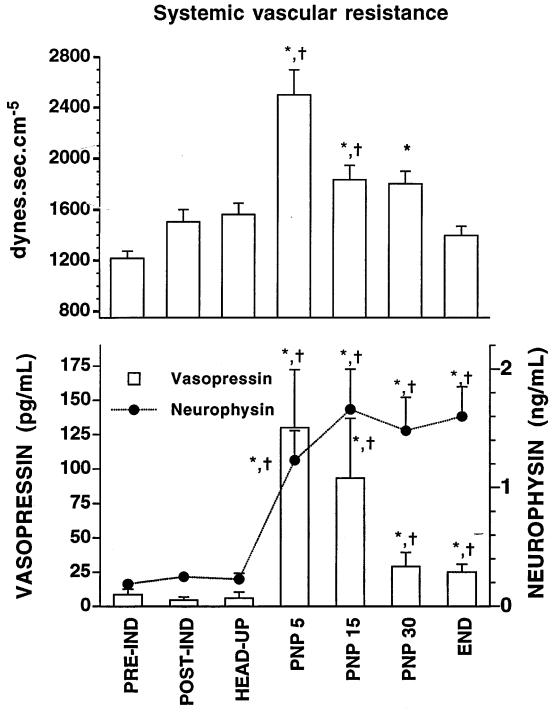
Metabolic changes during laparoscopic cholecystectomy: arterial PCO_2 ($PaCO_2$) and PO_2 (PaO_2), oxygen delivery (DO_2), oxygen consumption ($\dot{V}O_2$), mixed venous blood oxygen saturation ($S\bar{v}O_2$) and plasma concentration of lactate were measured at the same time points as in Table 1. Results are mean ± SEM. *$p < 0.05$ compared with before induction, †$p < 0.05$ compared with head-up tilt.

insufflation, and was associated with significant reductions in intraoperative isoflurane requirements. End-tidal isoflurane concentrations, 0.4 ± 0.1% before PNO in both groups, were increased to 0.9 ± 0.1% in the placebo group but were not changed in the clonidine group.

Profiles of hemodynamic changes were similar in studies 1 and 2. Clonidine smoothed some of these hemodynamic changes. Clonidine significantly reduced MAP and HR compared with placebo (Fig. 2). Moreover, clonidine attenuated the increase in MAP (placebo +28 ± 7 mm Hg versus clonidine +15 ± 5 mm Hg, $p = 0.07$) and significantly reduces the increase in SVR (placebo +745 ± 149 dynes·s·cm^{-5} versus clonidine +394 ± 113 dynes·s·cm^{-5}; $p < 0.005$) secondary to peritoneal insufflation after 5 min. However, no significant differences in absolute values of SVR (Fig. 2) were observed between the two groups. In both groups SVR did not change immediately after exsufflation, but it had significantly decreased 30 min after exsufflation. At this time point clonidine significantly reduced the postoperative increase in cardiac output. Finally, no significant differences in the remaining hemodynamic parameters (RAP, PCWP, PVR) were observed in the two groups. Mixed venous blood oxygen saturation remained normal in both groups intraoperatively. Thirty minutes after exsufflation, $S\bar{v}O_2$ in the clonidine group was >70% (74 ± 2%) and was significantly higher than in the placebo group (67 ± 4%).

Clonidine did not significantly affect the marked release of vasopressin observed immediately after peritoneal insufflation. Conversely, plasma concentrations of epinephrine and norepinephrine were significantly reduced in the clonidine group. Clonidine almost completely blocked the intraoperative increase of norepinephrine. Finally, clonidine had no effect on cortisol release (Fig. 3).

Figure 1. Changes in SVR as well as in plasma concentrations of vasopressin and neurophysin during laparoscopic cholecystectomy (study 1). Systemic vascular resistance was calculated and arterial blood samples were collected before the induction of anesthesia (PRE-IND); 10 min after the induction of anaesthesia (POST-IND); 10 min after tilting into a 10° head-up position (HEAD-UP); 5 min (PNP 5), 15 min (PNP 15) and 30 min (PNP 30) after the beginning of insufflation; and 30 min after exsufflation (END). Results are mean ± SEM. *$p < 0.05$ compared with PRE-IND; †$p < 0.05$ compared with HEAD-UP.



Discussion

These two studies confirm that peritoneal carbon dioxide insufflation to an intraabdominal pressure of 14 mm Hg produces significant hemodynamic changes in healthy patients. Pneumoperitoneum results in an increase in MAP, SVR and PVR and a decrease in cardiac output. Heart rate does not change, or increases only slightly. The increase in SVR is associated with a marked release of vasopressin and catecholamines. Clonidine given before PNO reduces this release of catecholamines and provides intraoperative hemodynamic stability.

Changes in cardiac output. In both studies cardiac output significantly decreased shortly after the beginning of peritoneal insufflation. The subsequent increase in cardiac output probably resulted from surgical stress, as reflected by increased concentrations of cortisol. Therefore, during PNO for opera-

Table 3. Endocrine Changes During Laparoscopy (Study 1)

	Before Induction	After Induction	Head Up	Pneumoperitoneum 5 min	Pneumoperitoneum 15 min	Pneumoperitoneum 30 min	After Surgery
Cortisol (μg/ml)	74 ± 9	65 ± 12	74 ± 15	91 ± 19	182 ± 16*†‡	248 ± 16*†‡	286 ± 25*†‡
Epi. (pg/ml)	68 ± 8	44 ± 4	46 ± 7	183 ± 39*†	236 ± 55*†	266 ± 96*†	389 ± 163*†
Norepi. (pg/ml)	241 ± 36	241 ± 32	295 ± 37	410 ± 46*†	530 ± 72*†‡	526 ± 63*†‡	508 ± 98*†
Renin (pg/ml)	16 ± 2	20 ± 4	34 ± 6*	42 ± 7*	53 ± 9*†‡	66 ± 11*†	48 ± 8†
Endothelin (fmol/ml)	246 ± 29	239 ± 19	237 ± 26	221 ± 25	233 ± 29	277 ± 36	272 ± 27
TxB_2 (pg/ml)	217 ± 34	266 ± 25	210 ± 32	215 ± 36	254 ± 34	310 ± 37	243 ± 40
$PGF_{1\alpha}$ (pg/ml)	204 ± 32	211 ± 23	162 ± 18	149 ± 20	198 ± 30	178 ± 26	165 ± 20
PGE_2 (pg/ml)	1,090 ± 83	1,154 ± 113	1,009 ± 113	912 ± 95	1,275 ± 108	1,045 ± 92	1,121 ± 110

Endocrine changes during laparoscopic cholecystectomy: arterial blood samples were collected at the same time points as in Table 1. The following hormones were measured: cortisol, epinephrine (Epi), norepinephrine (Norepi), renin, endothelin, a metabolite of thromboxane (TXB_2), a metabolite of prostacyclin (6-keto-$PGF_{1\alpha}$) and prostaglandin E_2 (PGE_2). Results are mean ± SEM. *$p < 0.05$ compared with before induction, †$p < 0.05$ compared with head-up tilt; ‡$p < 0.05$ compared with pneumoperitoneum 5 minutes.

tive laparoscopy, impairment of hemodynamic status occurs mainly at the beginning of peritoneal insufflation. Mixed venous blood oxygen saturation in both studies, as well as plasma lactate concentrations in study 1, remained normal intraoperatively. These findings suggest that changes in cardiac output occurring during PNO are well tolerated by healthy patients.

Because we only included healthy patients in this study, the decrease in cardiac output observed during PNO probably related to a reduction in preload. Pneumoperitoneum results in caval compression (18), an increase in venous resistance (19) and pooling of blood in the peripheral circulation (20). All these effects contribute to decreased venous return. A decline in venous return was confirmed by a reduction in left ventricular end diastolic volume, measured using transesophageal echocardiography (21). The paradoxical increase in RAP and PCWP after insufflation (2,4,22,23) can be explained by the increased intrathoracic pressure associated with PNO (4,11). Therefore, during PNO, RAP and PCWP can no longer be considered reliable indexes of cardiac filling pressures.

Increase in SVR. All studies reported to date describe an increase in SVR during PNO. This increase in afterload cannot be simply considered a reflex sympathetic response to decreased cardiac output. Indeed, SVR also increased in studies where no decrease in cardiac output was reported (24,25). Although the normal heart tolerates increases in afterload under physiologic conditions, the changes in afterload produced by PNO can result in deleterious effects in patients with cardiac diseases and may contribute to a further decrease in cardiac output (26). The increase in SVR is considered to be mediated by mechanical and neurohumoral factors (2,4,7), and the role of mechanical factors might not be predominant. Indeed, in the second study no changes in SVR were observed 5 min after exsufflation. Instead, correction of these hemodynamic changes was gradual and took several minutes, suggesting involvement of neurohumoral factors (2,7).

Table 4. Patient Data (Study 2)

	Placebo	Clonidine
N	9	11
Age (yrs)	51 ± 15	45 ± 15
Sex (F/M)	7/2	8/3
Weight (kg)	63 ± 8	70 ± 17
Height (cm)	164 ± 5	162 ± 23
PNO duration (min)	80 ± 35	67 ± 31
Preop. MAP (mm Hg)	96 ± 16	99 ± 8
Preop. HR (beats/min)	78 ± 15	80 ± 8
Preop. CO (L/min)	5.4 ± 1.5	4.8 ± 1.5

Data are mean ± SD. CO = cardiac output; HR = heart rate; MAP = mean arterial pressure; PNO = pneumoperitoneum. Mean arterial pressure (oscillometric arterial pressure) and heart rate were measured the day before surgery using a Datex AS/3 monitor. Cardiac output was measured by transthoracic echocardiography.

Endocrine correlates of the hemodynamic changes. The profile of vasopressin release in the first study correlated most closely with changes in SVR. Induction of PNO resulted in a rapid and marked release of vasopressin in both studies. This finding was confirmed by the release of neurophysin. The longer half-life of neurophysin explains why plasma neurophysin concentrations plateaued after the induction of PNO. Increases in plasma vasopressin levels were correlated with changes in intraabdominal pressure, intrathoracic pressure and transmural RAP (11). Mechanical stimulation of peritoneal receptors also resulted in increases of vasopressin release (27), SVR and arterial pressure (28). However, whether increasing intraabdominal pressure to 14 mm Hg is sufficient to stimulate these receptors is unknown. Plasma concentrations of vasopressin measured in our two studies were high, and of a magnitude similar to those reported during acute hemodynamic stimulation (e.g., massive hemorrhage). This is important because vasopressin is a potent vasopressor even at normal physiologic concentrations (29). Other mediator(s) are implicated in the increase in SVR. Indeed, although clonidine did not significantly affect plasma vasopressin concentrations, it attenuated the increase in SVR.

Catecholamines, and more particularly norepinephrine, which was also released early during PNO, might contribute to the increase in afterload. Accordingly, clonidine, which significantly reduced the release of catecholamines and almost

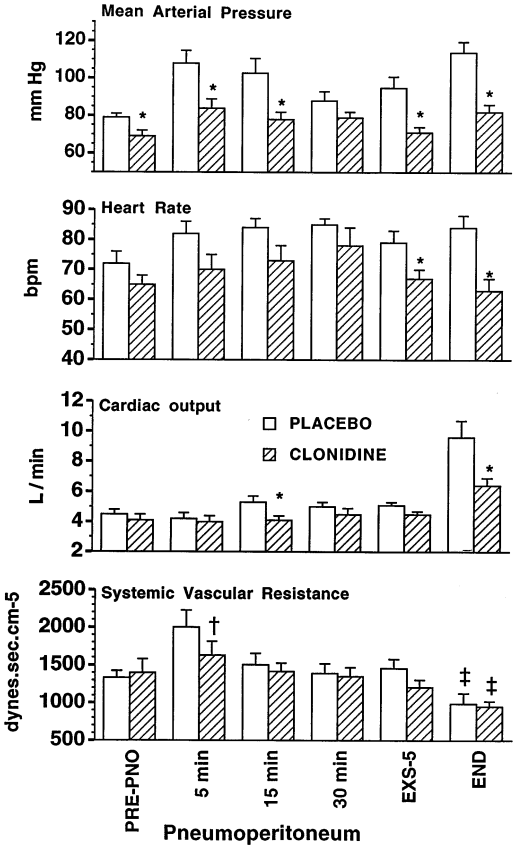


Figure 2. Effect of 8 μg/kg clonidine infused over 1 h before peritoneal insufflation on hemodynamic changes induced by carbon dioxide PNO (study 2). Mean arterial pressure, heart rate, cardiac output and systemic vascular resistance were measured or calculated at the end of the infusion of clonidine or placebo and before the creation of the PNO (PRE-PNO); 5 min after the beginning of peritoneal insufflation with the patient in the supine position; 15 and 30 min after the beginning of insufflation with the patient tilted to a 10° head-up position; 5 min after exsufflation with the patient still tilted to a 10° head-up position (EXS-5); and finally 30 min after exsufflation, approximately 15 min after the end of anesthesia and tracheal extubation with the patient in a horizontal position breathing spontaneously (END). Results are mean ± SEM. *$p < 0.05$ compared with placebo; †the increase in SVR was significantly ($p < 0.05$) less in the clonidine group (+394 ± 113 dynes·s·cm^{-5}) than in the placebo group (+745 ± 49 dynes·s·cm^{-5}); ‡$p < 0.05$ compared with PNO 30 min.

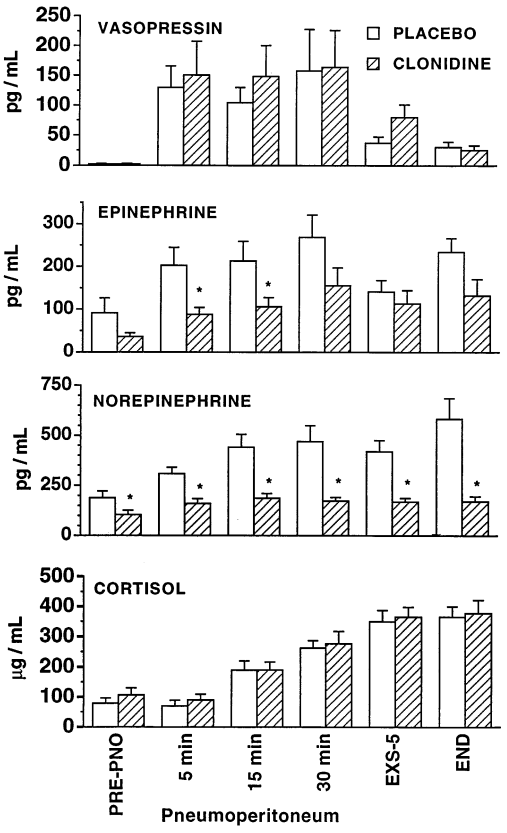


Figure 3. Effect of 8 μg/kg clonidine infused over 1 h before peritoneal insufflation on endocrine changes induced by carbon dioxide PNO (study 2). Vasopressin, epinephrine, norepinephrine and cortisol were measured at the same time points as in Figure 2. Results are mean ± SEM. *$p < 0.05$ compared with placebo.

completely blocked norepinephrine release, attenuated the increase in SVR. The stimulus for catecholamine release during PNO cannot be determined from these studies. Hypercarbia and surgical stress were probably not causes of the initial increase in epinephrine and norepinephrine because $PaCO_2$ was kept within physiologic limits, and plasma cortisol levels had not yet changed at 5 min of PNO in both studies. The gradual increase in plasma catecholamine concentrations observed later intraoperatively may be correlated with surgical stress, as reflected by increasing plasma concentrations of cortisol, and may contribute to the intraoperative improvement of cardiac output.

In study 1 the plasma concentration of renin was already increased before insufflation, probably in response to decreased venous return secondary to the head-up position and subsequent hypotension. Five minutes after the beginning of insufflation, even though SVR had reached its peak, no significant further increase was observed. The contribution of renin to the initial increase in afterload is therefore questionable. During PNO the progressive increase in plasma renin concentration might be related to activation of the sympathetic system and to surgical stress (30). Furthermore, renin secretion may also result from reduction of glomerular filtration and renal plasma flow induced by PNO (31,32). Finally, prostacyclin, PGE_2, TxB_2 and endothelin did not seem to contribute to the hemodynamic changes induced by PNO.

Effects of clonidine on hemodynamic and endocrine changes. In the second study we used clonidine to modulate hormone release, more particularly catecholamines and vasopressin, with an aim to improving our understanding of the pathogenesis of the hemodynamic changes induced by PNO. Clonidine improves intraoperative and postoperative hemodynamic stability during laparoscopy, similar to what is seen during general surgery (33,34). Clonidine smoothed the changes in arterial pressure, HR, SVR and cardiac output. These benefits are mediated by a reduction of neurohormonal

secretion secondary to stress-induced sympathoadrenal hyperactivation (33–36). Accordingly, plasma catecholamine concentrations were significantly lower in the clonidine group. Inversely, clonidine had no effect on cortisol or vasopressin release in our study. The effect of clonidine on plasma cortisol levels seems to be controversial in humans (37–42). However, stress-induced release of cortisol (40–42), such as during anesthesia and surgery (42), is not affected by clonidine. The effect of clonidine on vasopressin secretion is also controversial (35). Differences in species, route of administration and doses may explain these discrepancies. Because the characteristics of vasopressin release depend on the factor triggering its release (changes in osmolarity, hypovolemia, hypotension, etc.) (43), the effect of clonidine on vasopressin might also be stimulus specific. Nevertheless, our findings suggest that high doses of clonidine given intravenously have no effect on vasopressin release during laparoscopy. Because clonidine potentiates anesthetic agents (33,35,44), isoflurane requirements were significantly reduced in the clonidine group.

Effects of fluid load on hemodynamic changes. Comparison of our two studies confirms the influence of intravascular volume status on the hemodynamic changes induced by PNO (19,45,46). Compared with the patients of study 1, patients of study 2 were preloaded with 500 ml lactated Ringer's solution, and insufflation was performed in the supine position instead of the head-up position. Although cardiac output and SVR were similar in study 1 after the induction of anesthesia and in the placebo group of study 2 before induction of PNO (Table 1, Fig. 2), PNO after 5 min resulted in a greater decrease in cardiac output in study 1 (36 ± 5% in study 1 versus 7 ± 5% in study 2) and a higher increase in SVR in study 1 (71 ± 9% in study 1 versus 57 ± 10% in study 2). Subsequently, cardiac output remained lower and SVR greater in study 1 than in study 2, despite similar levels of anesthesia (isoflurane concentrations were similar in both studies). These results provide further evidence that increasing cardiac filling pressures before peritoneal insufflation by fluid loading, followed by tilting the patient to the head-up position only after insufflation, attenuates hemodynamic changes induced by PNO.

In conclusion, the carbon dioxide PNO required for laparoscopy results in multiple hemodynamic changes. These changes were, however, well tolerated by healthy patients. Pneumoperitoneum induced increases in arterial pressure and systemic and pulmonary vascular resistances and a decrease in cardiac output. Both mechanical (increased intraabdominal pressure) and humoral factors contributed to these changes. Vasopressin and catecholamine release probably mediated the increase in SVR. Clonidine and fluid loading before peritoneal insufflation attenuated these hemodynamic changes. Further studies are needed to determine the ideal dose of clonidine. This information should be helpful in safely managing high-risk cardiac patients, thereby allowing these patients to benefit from all the postoperative advantages of the laparoscopic approach.

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