Hormonal responses and cardiac filling pressures in head-up or head-down position and pneumoperitoneum in patients undergoing operative laparoscopy

E. A. HIRVONEN, L. S. NUUTINEN AND O. VUOLTEENAHO

Summary

In order to determine if there are differences in stress responses, as reflected in neuroendocrine activation, we have compared data from two groups of patients undergoing laparoscopic surgery either in the head-up position for cholecystectomy or in the head-down position for hysterectomy. Arterial blood samples were obtained for measurement of serum concentrations of cortisol, catecholamines, renin activity and atrial natriuretic peptide (measured as N-terminal peptide of proANP), and haemodynamic data (pulmonary capillary wedge pressure, PCWP) were collected at the following times: in awake patients, supine at rest (baseline); in awake patients in the position used during surgery; during laparoscopy; and 2 h after surgery. The same anaesthetic technique and normocapnic mechanical ventilation were used in both groups. There were no significant differences between groups in cortisol or adrenaline concentrations, or in renin activity. There was, however, a three-fold increase in cortisol towards the recovery period in both groups. Noradrenaline concentrations increased more in the head-up group suggesting increased sympathetic nervous activity. In awake patients, plasma NT-proANP concentrations were significantly higher in the head-down tilt compared with the head-up position, and NT-proANP correlated well with PCWP. During pneumoperitoneum, however, NT-proANP concentrations remained low in spite of increased PCWP suggesting that inflation of the abdomen interferes with venous return. In conclusion, abdominal surgical laparoscopy in both the head-up and head-down positions caused marked activation of neuroendocrine responses. The two surgical positions, however, differed in their effect on the circulation. In awake patients, head-down tilt was associated with increased concentrations of plasma NT-proANP, indicating increased venous return and atrial stretch.

Key words

Nociceptive surgical stimulation is accompanied by activation of the hypothalamic–pituitary–adrenal (HPA) axis and by increased activity of the sympathetic nervous system, which is generally referred to as the stress response to surgery. It is believed commonly that the magnitude of the response is related directly to the size of the wound.1 On the basis of clinical experience, minimal-access techniques in abdominal surgery are associated with less postoperative stress than conventional surgery. Recent reports concerning laparoscopic cholecystectomy have, however, indicated that the stress response, as measured by intraoperative release of cortisol and catecholamines, is not diminished by the laparoscopic approach and may even be increased in comparison with the open technique.2–5 The stress response to surgery can be modified by anaesthesia,6 surgical positioning7 and probably by the site of the operation.8

Three major neurohumoral systems are involved in maintaining arterial pressure and circulating volume: sympathetic nervous system, renin–angiotensin–aldosterone system (RAA) and the vasopressin system.9,10 These vasopressor systems are Counterbalanced by atrial natriuretic peptide (ANP) in the regulation of circulating volume and arterial pressure.11,12 The major stimulus for ANP secretion from the atrium is atrial stretch caused by increased atrial transmural pressure.13 An increase in atrial cavity pressure without an increase in atrial transmural pressure (as with cardiac tamponade) does not trigger ANP release.13 During laparoscopic procedures, creation of pneumoperitoneum increases right and left atrial intraluminal pressures.14–16 There are conflicting views on whether or not increased central pressures represent increased central blood volume or increased intrathoracic pressure caused by pneumoperitoneum.14–16

The neuroendocrine responses to upper and lower abdominal operative laparoscopy have not been compared. Although similar, the two have significant procedural differences. The first aim of this study

EILA A. HIRVONEN, MB, Department of Anaesthesiology, Kuopio University Hospital, SF-70210 Kuopio, Finland. LAURI S. NUUTINEN, MD, PHD (Department of Anaesthesiology); OLLI VUOLTEENAHO, MD, PHD (Department of Physiology); Oulu University, SF-90020 Oulu, Finland. Accepted for publication: October 31, 1996. Correspondence to E. A. H.
therefore was to determine if neuroendocrine responses associated with upper and lower abdominal laparoscopy have clinically relevant differences. Second, we examined the correlation between changes in cardiac filling pressures and release of ANP.

Patients and methods
The study was approved by the Ethics Committee of Kuopio University Hospital and Kuopio University, and written informed consent was obtained from each patient. We studied 16 ASA I–II patients undergoing elective laparoscopic cholecystectomy (LC group) and 19 ASA I–II patients undergoing elective laparoscopic hysterectomy (LH group). Patients with significant cardiovascular, hepatic or renal disease, and those using some angiotensin converting enzyme inhibitors were excluded.

All patients were premedicated with diazepam 10–15 mg orally. Patients also received their usual morning medication, if any, except diuretics. After transfer to the operating theatre, i.v. infusion of 0.9% NaCl solution was started at a rate of 5 ml kg⁻¹ h⁻¹ for 1 h and continued at a rate of 2.5 ml kg⁻¹ h⁻¹ thereafter. A radial artery cannula and a 7.5-French gauge thermodilution pulmonary artery catheter for haemodynamic measurements and blood sampling were introduced under local anaesthesia. Mean arterial pressure (MAP), mean central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP) and cardiac output (CO) were recorded by a haemodynamic monitor (AS3, Datex Corp., Finland). The monitor calculated cardiac index (CI = CO/body surface area) and systemic vascular resistance index (SVRI = (MAP – CVP) × 80/CI). The pressure transducers were located at the level of the right atrium. Haemodynamic data were collected simultaneously with blood sampling.

ANAESTHESIA AND SURGERY
The same anaesthetic technique was used in all patients. Anaesthesia was induced with glyco-pyrrollium 0.004 mg kg⁻¹, diazepam 2.5–10 mg, thiopentone (mean 3.9 mg kg⁻¹), fentanyl 0.1 mg and vecuronium 0.1 mg kg⁻¹. After tracheal intubation, general anaesthesia was maintained with up to 1 MAC of isoflurane and 35% oxygen in an oxygen–air mixture. Additional doses of fentanyl 0.05–0.1 mg and vecuronium 1–2 mg were given when needed. An extra i.v. infusion of colloid solution (6% hydroxyethyl-amylopectinase, Plasmafusin, Pharmacia) in 250-ml doses up to 500 ml was given if PCWP was less than 4 mm Hg before laparoscopy. During anaesthesia minute ventilation was adjusted to maintain end-tidal P\text{CO}_2 at 4.5–5.0 kPa by controlled mechanical ventilation. Pneumoperitoneum for laparoscopy was produced with a Verres’ needle using a carbon dioxide insufflator, and intra-abdominal pressure was maintained automatically at the desired level (13–16 mm Hg, recorded by the insufflator). All operations were performed successfully by the laparoscopic approach. Six hysterectomy patients experienced haemorrhage (more than 200 ml) during operation (range 300–1000 ml). Blood loss was replaced with 6% hydroxyethyl-amylopectinase (Plasmafusin, Pharmacia) and red blood cells. During the first 2 h in the recovery room, fentanyl 0.05 mg i.v. was administered for pain when needed.

BLOOD SAMPLING
Baseline arterial blood samples were obtained approximately 30 min after catheterization with the patient resting in bed (baseline). Subsequent awake samples were obtained at 5 min after placing the patient on the operating table to the position used during laparoscopy: 15–20° head-up for cholecystectomy or 25–30° head-down for hysterectomy. Blood samples during surgery were obtained at the end of laparoscopy before desufflation of the intra-abdominal gas and with the patient still in the head-up or head-down position. Postoperative blood samples were obtained 2 h after surgery in the recovery room.

ASSAYS
Blood for adrenaline and noradrenaline assays was collected in ice-chilled vacuum tubes containing glutathione and ethylene-glutamine-tetra-acetic acid, for renin and NT-proANP assays in ice-chilled tubes containing EDTA, and for cortisol measurements in plain serum tubes. Samples for plasma separation were centrifuged within 10 min and stored at −20°C (for catecholamine assays at −70°C) until analysed. Blood samples for cortisol measurement were handled as above after clotting.

Adrenaline and noradrenaline concentrations in plasma were analysed by high performance liquid chromatography with coulometric detection, as described in detail elsewhere. The detection limits of adrenaline and noradrenaline were 0.1 nmol litre⁻¹ and 0.075 nmol litre⁻¹, respectively. Intra- and inter-assay coefficients of variations (cv) for adrenaline were 11% and 11% at 0.26 nmol litre⁻¹ and for noradrenaline, 7.8% and 15.2% at 1.42 nmol litre⁻¹, respectively. The normal ranges for adrenaline and noradrenaline are 0.32 (0.19) nmol litre⁻¹ and 0.98 (0.27) nmol litre⁻¹, respectively. Cortisol concentrations in serum were determined with a commercially available direct radioimmunoassay (Orion Diagnostica Cortisol [H9262], Orion Co, Turku, Finland). The sensitivity of the method (the smallest detectable concentration) is approximately 4–7 nmol litre⁻¹, the intra-assay cv is 2.1–4.1% and the inter-assay cv is 4.3–9.0% within the measurement range; the normal range for morning concentrations is 150–650 nmol litre⁻¹. Plasma renin activity was measured with the Medix Angiotensin I Test (Medix Biochemica Corporation, Kauniainen, Finland). The detection limit of the assay was <0.2 μg litre⁻¹ h⁻¹ (normal range 0.9–2.0 μg litre⁻¹ h⁻¹). Intra- and inter-assay cv were 15.4% and 7.7% at 1.0 μg litre⁻¹ h⁻¹, 8.9% and 5.6% at 3.3 μg litre⁻¹ h⁻¹, and 8.7% and 2.6% at 7.8 μg litre⁻¹ h⁻¹, respectively.

NT-proANP was assayed directly from plasma as
follows. Standards and samples (25 μl) in duplicate were incubated with 200 μl of radioiodinated NT-proANP and 200 μl of rabbit anti-human NT-proANP antiserum (final dilution 1/40 000) overnight at +4°C. Bound and free fractions were separated by double antibody precipitation in the presence of polyethylene glycol. The sensitivity of the assay was 0.75 fmol/tube, the inter-assay cv was 5.3% at 0.275 nmol litre⁻¹ and 9.3% at 0.128 mol litre⁻¹. The antisera react correctly with proANP₁–126 and proANP₁–98 but does not recognize ANP (proANP₉₉–₁₂₆), B-type natriuretic peptide or C-type natriuretic peptide (cross reaction <0.01%). Basal plasma concentration of NT-proANP in healthy adults is 0.355 (0.123) nmol litre⁻¹.

STATISTICAL ANALYSIS

Results are expressed as mean (SEM), except patient data, which are given as mean (SD) and range. Correlations between variables are reported by the Pearson correlation coefficients. All statistical analyses were performed with a statistical software package (SPSS/PC+, SPSS Inc., Chicago, IL, USA). Data were analysed by one- and two-way analysis of variance for repeated measurements. Statistically significant differences were isolated by means of the paired Student’s t test (within group) and by the unpaired Student’s t test (between groups). The relationships between NT-proANP and CVP, and between NT-proANP and PCWP were studied by linear regression analysis. The level of significance was P<0.05 unless otherwise indicated.

Results

There were no significant differences in patient characteristics between the laparoscopic cholecystectomy (LC) and laparoscopic hysterectomy (LH) groups (table 1). Laparoscopy was more prolonged in the LH group than in the LC group.

There were no significant differences between the two groups in any of the hormones measured under awake baseline conditions (fig. 1). Noradrenaline concentration increased both in the head-up and head-down positions. The decrease in NT-proANP in the head-up position and the increase in NT-proANP in the head-down position were not significant compared with baseline, but the difference between the LC and LH groups was significant (P<0.006).

Laparoscopy with carbon dioxide pneumoperitoneum increased serum cortisol to concentrations more than two times higher than those detected before surgery. Plasma noradrenaline increased in both groups, but concentrations were significantly higher in the LC group than in the LH group.

<table>
<thead>
<tr>
<th>Table 1: Patient characteristics and duration of laparoscopy, surgery and anaesthesia (mean (sd) [range])</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cholecystectomy</strong></td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
</tr>
<tr>
<td><strong>Body surface area (m²)</strong></td>
</tr>
<tr>
<td><strong>Body mass index (kg m⁻²)</strong></td>
</tr>
<tr>
<td><strong>Duration of laparoscopy (min)</strong></td>
</tr>
<tr>
<td><strong>Duration of operation (min)</strong></td>
</tr>
<tr>
<td><strong>Duration of anaesthesia (min)</strong></td>
</tr>
</tbody>
</table>

Figure 1  Mean (SEM) plasma concentrations of adrenaline, noradrenaline, cortisol and NT-proANP, and renin activity in laparoscopic cholecystectomy (■) and laparoscopic hysterectomy (□) patients at baseline (B), during awake head-up or head-down positioning (P), during laparoscopy (L) and during recovery (R). The arrows indicate significant differences between the cholecystectomy and hysterectomy groups: *P<0.05 compared with previous values, †P<0.05 compared with baseline values.
Hormones and operative laparoscopy

Plasma adrenaline increased in both groups, but plasma renin activity (PRA) increased only in the LC group during laparoscopy compared with baseline. Plasma NT-proANP concentrations were higher in the LC group and lower in the LH group during laparoscopy compared with awake values in the same surgical position. NT-proANP concentrations during laparoscopy were not significantly different from baseline awake concentrations.

At 2 h after surgery, serum cortisol concentrations increased further from laparoscopic concentrations in the LH group. Plasma adrenaline concentrations were still above baseline in both groups. In the LH group plasma noradrenaline concentrations were increased above baseline, but in the LC group they had returned to near baseline. Plasma NT-proANP concentrations were increased above laparoscopic and baseline concentrations after surgery in the LC group ($P=0.01$).

MAP and SVRI increased, and cardiac index (CI) decreased, both in the head-up and head-down positions in awake patients (table 2). PCWP and CVP decreased in the head-up position and increased in the head-down position. During laparoscopy, CI decreased and SVRI increased compared with baseline in both groups. Pneumoperitoneum increased PCWP and CVP in head-up laparoscopy, but in head-down laparoscopy only CVP increased further compared with the same position in awake patients. During recovery, most of the values approached baseline, although CI, PCWP and CVP remained increased in the LC group.

For all patients grouped together ($n=35$), linear correlations between NT-proANP and PCWP were poor under baseline conditions ($r=0.06, P=0.75$).
and during laparoscopy \((r=0.27, P=0.11)\). However, during awake head-up or head-down positions and during recovery, correlations were significant \((r=0.60, P=0.0002, and r=0.40, P=0.017, respectively)\). Similar correlations (with slightly lower \(r\) values) were found between NT-proANP and CVP, with correlation coefficients of 0.04, 0.27, 0.48, and 0.32 at baseline, during laparoscopy, during awake head-up or head-down positions and during recovery, respectively. The possible effect of blood loss in the LH group on NT-proANP values during laparoscopy and recovery was examined, and no significant correlations were found \((P=0.79, P=0.44)\).

Figure 2 shows the linear correlations between NT-proANP and PCWP during the different phases of the study.

**Discussion**

We have demonstrated that laparoscopy either in the head-up position during cholecystectomy or in the head-down position during hysterectomy caused marked activation of neuroendocrine responses, reflected by increases in serum cortisol and plasma catecholamine concentrations. We found no significant differences between upper and lower abdominal surgical laparoscopy in serum cortisol or plasma adrenaline concentrations or in plasma renin activity. Plasma noradrenaline concentrations were significantly higher in the cholecystectomy patients which may not be an unexpected result considering the prominent sympathetic sensory innervation of the upper abdomen. Varying the surgical position may also have contributed to the difference. Head-down tilt compared with the supine position during lower abdominal surgery has been reported to be associated with decreased sympathetic nervous system activity and lower plasma noradrenaline concentrations.\(^7\) Further, higher noradrenaline secretion has generally been found in the upright compared with the supine position in awake volunteers.\(^19\)

NT-proANP is secreted from the heart in equimolar quantities with the biologically active ANP. It is, however, a much more stable peptide in the circulation than ANP, which is eliminated rapidly from blood by receptor binding and enzymatic degradation.\(^18\) The close correlation between NT-proANP and ANP has been demonstrated previously in patients with cardiac disease.\(^20\) Stretch of cardiac atria is the most potent stimulus for the ANP system, and PCWP and CVP have been shown to correlate positively with release of natriuretic peptides from the atria.\(^20\)\(^22\) Our results, however, showed that during pneumoperitoneum there was a poor correlation between the activity of the ANP system, as reflected by plasma NT-proANP concentrations, and measured intraluminal cardiac filling pressures, reflected by PCWP and CVP. The unchanged NT-proANP concentrations, in spite of increased filling pressures during pneumoperitoneum, indicate the surprising conclusion that atrial transmural pressures do not increase during the procedure. Inflation of the abdomen associated with the laparoscopic technique may interfere with venous return, thus counteracting the increase in central blood volume otherwise resulting from the head-down tilt.

Plasma ANP concentrations have been shown to decrease or remain stable after severe blood loss in animals.\(^23\)\(^24\) In contrast, moderate blood loss (up to 1000 ml) in healthy volunteers did not induce significant decreases in ANP release.\(^25\) Some patients in our hysterectomy group experienced haemorrhage up to 1000 ml. Blood loss was replaced with colloid solutions and red blood cells, and the continuously monitored patients did not show signs of hypovolaemia at any phase of the study.

Despite the fact that the magnitude of the neuroendocrine response appeared to be correlated directly with the extent of the surgical wound\(^1\) and that minimal access techniques appeared to cause less postoperative stress than conventional surgery, intraoperative increases in circulating cortisol and catecholamine concentrations have been shown to be similar\(^2\)\(^-\)\(^4\) or even larger\(^5\) with the laparoscopic compared with the open technique. Cooper and co-workers showed that even short-duration gynaecological laparoscopy produced significant hormonal and glycaemic responses.\(^26\) This is in keeping with our results in which both upper and lower abdominal laparoscopic surgery were associated with clear activation of the HPA axis and the catecholamine system.

**References**