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ASSESSMENT OF SERUM CATECHOLAMINE CONCENTRATIONS IN PATIENTS WITH PHEOCHROMOCYTOMA UNDERGOING VIDEOLAPAROSCOPIC ADRENALECTOMY

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ABSTRACT

Introduction: We analyzed the changes in serum catecholamine concentrations, i.e. adrenaline and noradrenaline, in response to surgical stress in patients with pheochromocytoma who undergone videolaparoscopic adrenalectomy.

Materials and Methods: Between January 1998 and March 2002, 11 patients underwent 12 videolaparoscopic adrenalectomies. In one case, the adrenalectomy was bilateral. Serum catecholamines were measured at 6 surgical times: T0: control before induction; T1: following the induction, laryngoscopy and intubation sequence; T2: after installing the pneumoperitoneum; T3: during manipulation-exeresis of the pheochromocytoma; T4: following ablation of the pheochromocytoma; T5: in the recovery room following intervention when the patient was extubated and was hemodynamically stable.

Results: Mean concentrations of serum noradrenaline were significantly different when the T0 and T2 surgical times were compared (T0: 3161 pg/mL; T2: 40440 pg/mL; $p < 0.01$), T0 and T3 (T0: 3161 pg/mL; T3: 46021 pg/mL; $p < 0.001$), T1 and T3 (T1: 5531 pg/mL; T3: 46021 pg/mL; $p < 0.01$), T2 and T4 (T2: 40440 pg/mL; T4: 10773 pg/mL; $p < 0.01$) and T3 and T5 (T3: 46021 pg/mL; T5: 2549 pg/mL; $p < 0.001$). Mean concentrations of serum adrenaline were significantly different when the T0 and T3 surgical times were compared (T0: 738 pg/mL; T3: 27561 pg/mL; $p < 0.01$).

Conclusion: The pneumoperitoneum significantly increases serum noradrenaline concentrations, manipulation of the adrenal gland significantly increases the serum concentrations of noradrenaline and adrenaline, and the pheochromocytoma ablation significantly decreases serum noradrenaline concentrations.

Key words: pheochromocytoma; laparoscopy; catecholamines
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INTRODUCTION

Pheochromocytoma is an uncommon and important neoplasia because, despite its rarity, it is associated with catecholamine-induced hypertension, which can be resolved by neoplasia excision. The definitive treatment for pheochromocytoma is surgical ablation of the adrenal gland and/or paragangliomas. Before the 1950s, the peroperative mortality was between 20 and 25% of cases with a preoperative diagnosis of pheochromocytoma and around 50% of cases without a preoperative diagnosis of pheochromocytoma. The lack of proper control for hypertensive crises and cardiac arrhythmias during manipulation and ablation of the pheochromocytoma was responsible for this high mortality. The advances in peroperative control and the preoperative introduction of alpha 1-adrenergic blockade have significantly reduced mortality rates (1).

The first laparoscopic adrenalectomies were described by Gagner et al. and Higashihara et al. in 1992 (2,3). Studies have shown that videolaparoscopic adrenalectomy offers lower morbidity than open surgery (4,5). The videolaparoscopic technique has become the preferred option for treating adrenal tumors (6), however some doubts remain about the use of videolaparoscopy for management of pheochromocytomas due to cardiovascular risks that are potentially higher when compared to open surgery. Such risks are related to catecholamine release. Factors such as the use of carbon dioxide, the increase in abdominal tension and manipulation of the adrenal gland have been implied in catecholamine release (7).

Thus, in order to validate the videolaparoscopic technique in the management of pheochromocytomas, it is important to determine potential changes in serum catecholamine concentrations, as well as the relationship between such changes and higher cardiovascular risk.

This study aimed to assess changes in serum catecholamine concentrations, i.e. adrenaline and noradrenaline, in response to surgical stress in patients with pheochromocytoma undergoing videolaparoscopic adrenalectomy.

MATERIALS AND METHODS

The study was performed between January 1998 and March 2002 in 11 patients undergoing 12 videolaparoscopic adrenalectomies. The study included patients diagnosed with pheochromocytoma, which was confirmed through dosing of serum and urinary catecholamines. Abdominal and pelvic computerized tomography was performed in 8 patients, magnetic resonance imaging in 10 patients and scintigraphy with ^{131}I-metaiodobenzylguanidine in 10 patients.

Blood collections for dosing catecholamines, adrenaline and noradrenaline, by high-pressure liquid chromatography (HPLC) were performed at the following times: T0: control before induction; T1: following the induction, laryngoscopy and intubation sequence; T2: during the creation of pneumoperitoneum; T3: during manipulation-extraction of the pheochromocytoma; T4: following ablation of the pheochromocytoma; T5: in the recovery room following the intervention when the patient was extubated and hemodynamically stable.

All patients underwent preoperative cardiovascular assessments, including Doppler echocardiography and 24-hour Holter. Preparation started 15 days before the intervention by associating a alpha 1 blocker (prazosin: alpress® LP 5 mg/day) and a beta 1 blocker (bisoprolol: détensil® 10 to 20 mg/day). Three days before the intervention, an intravenous alpha 1 blocker, urapidil® (250 mg/day in continuous perfusion and hourly control of blood pressure), was started as a replacement to oral therapy and maintained until the end of the intervention. Oral pre-anesthetic medication consisted of 5 mg midazolam (short-acting benzodiazepine) associated with 0.5 mg atropine (muscarinic receptor blocker).

General anesthesia was standardized as follows: induction with propofol (2-2.5 mg/Kg^{-1}) and sufentanil (0.8-1 μg/Kg^{-1}) IV for control of blood pressure (BP), orotracheal intubation facilitated by cisatracurium 0.15 mg.Kg^{-1}; maintenance with continuous perfusion of sufentanil and cisatracurium and administration of sevoflurane or isoflurane with pure oxygen. Following induction, BP was continuously monitored using an arterial catheter connected to a blood pressure meter (Baxter^{tm}). Hydration was started with crystalloids 10-15 mL/Kg^{-1}/h^{-1} (isotonic saline solution, Ringer solution). Ventilation was adapted in order to maintain the PCO_2 between 35 and 45 mmHg. Urapidil was maintained in a continuous infusion of 10 mg/h^{-1} until ligation of the adrenal vein. Tension peaks were defined as systolic blood pressure (SBP) over 160 mmHg, and were treated through administering nicardipine (2-4 mg) aiming to maintain SBP between 120-160 mmHg. Episodes of sinus tachycardia, as defined by a heart rate (HR) over 100-120 b/min^{-1}, were treated by the administration of esmolol 100 mg in order to maintain the HR under 100 b/min^{-1}. Cardiovascular shock, as defined by SBP lower than 80 mmHg, was treated by administering ephedrine 3-6 mg IV.

The adrenalectomies were performed as described by Rocha et al., 2003 (8). Patients were positioned in lateral decubitus opposite the lesion. Four trocars were used - 3 10-mm and one 5-mm. The first trocar (10 mm) was introduced by "open" laparoscopy to the lateral margin of the rectus muscle of the abdomen approximately 4 cm cranial to the umbilical scar. The second trocar (10 mm) was placed on the epigastric midline. The third trocar (10 mm) was placed lateral to the first trocar, between the lateral margin of the rectus muscle of the abdomen and the anterior axillary line. The fourth trocar (5 mm) was placed lateral to the third trocar, between the anterior axillary line and the middle axillary line. The pneumoperitoneum was maintained at 12 mmHg. When the left adrenal gland was operated on, the intra-abdominal procedure started with an incision in the parietocolic gutter and dissection of two thirds of the descending colon. The spleen was withdrawn to expose the upper region of the renal cavity. The left renal vein was dissected and the adrenal vein was then identified, dissected and sectioned with metallic clips. Following this, the adrenal gland was dissected on the cleavage plane between the adrenal gland and the kidney. Arteries and occasional small accessory veins were sectioned with clips or after bipolar coagulation around the gland. The adrenalectomy specimen was removed inside an endosac (Endocath 10®) through a trocar orifice that was enlarged by 1 cm on each side. The trocar orifices were closed in 2 planes. When the right adrenal gland was operated on, the right liver lobe was withdrawn after sectioning of the triangular ligament. The renal cavity was exposed above the right colic angle. The cava vein was dissected up to the adrenal vein, which was then sectioned with clips. The following surgical times were similar to the left adrenalectomy.

The ligation of the adrenal vein was performed early, with minimal previous dissection of the adrenal gland.

To statistically analyze the results, Graphpad Prism software was employed, using non-parametric methods: Kruskal-Wallis test and Dunn's multiple comparisons test.

The statistical significance value was established at 95 % ($p < 0.05$).

RESULTS

No surgical conversion was required. The mean length of intervention was 127 min (75 to 195 min). Blood loss was between 0 and 1000 mL with a mean value of 105 mL.

The mean serum noradrenaline concentrations were significantly different ($p < 0.05$) when comparing T0 and T2 surgical times (T0: 3161 pg/mL; T2: 40440 pg/mL; $p < 0.01$), T0 and T3 (T0: 3161 pg/mL; T3: 46021 pg/mL; $p < 0.001$), T1 and T3 (T1: 5531 pg/mL; T3: 46021 pg/mL; $p < 0.001$), T2 and T4 (T2: 40440 pg/mL; T4: 10773; $p < 0.01$) and T3 and T5 (T3: 46021 pg/mL; T5: 2549 pg/mL; $p < 0.001$). There was no statistical difference ($p > 0.05$) when the other surgical times were compared (Figure-1).

Mean serum adrenaline concentrations were significantly different when comparing the T0 and T3 surgical times (T0: 738 pg/mL; T3: 27561 pg/mL; $p < 0.01$). There was no statistical difference ($p > 0.05$) when the other surgical times were compared (Figure-2).

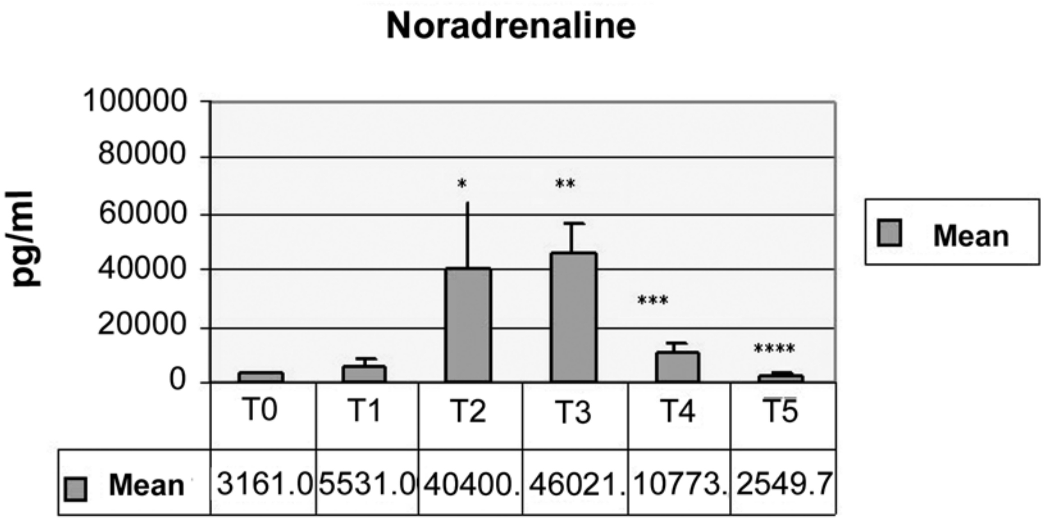
During the creation of the pneumoperitoneum (T2), 6 hypertension peaks were observed, which were associated with sinus tachycardia in 3 cases. Manipulation or exeresis of the adrenal gland (T3) caused 8 hypertension peaks associated with sinus tachycardia in 2 cases.

Patient 5 presented atrial and ventricular extrasystoles during these 2 surgical times (T2 and T3) and was treated with intravenous (IV) esmolol.

The therapeutic outcome was reached in all cases, with SBP decreasing from 178 +/- 12 to 129 +/- 11 mmHg ($p < 0.001$) and diastolic blood pressure (DBP) from 99 +/- 13 to 73 +/- 11 mmHg ($p < 0.001$).

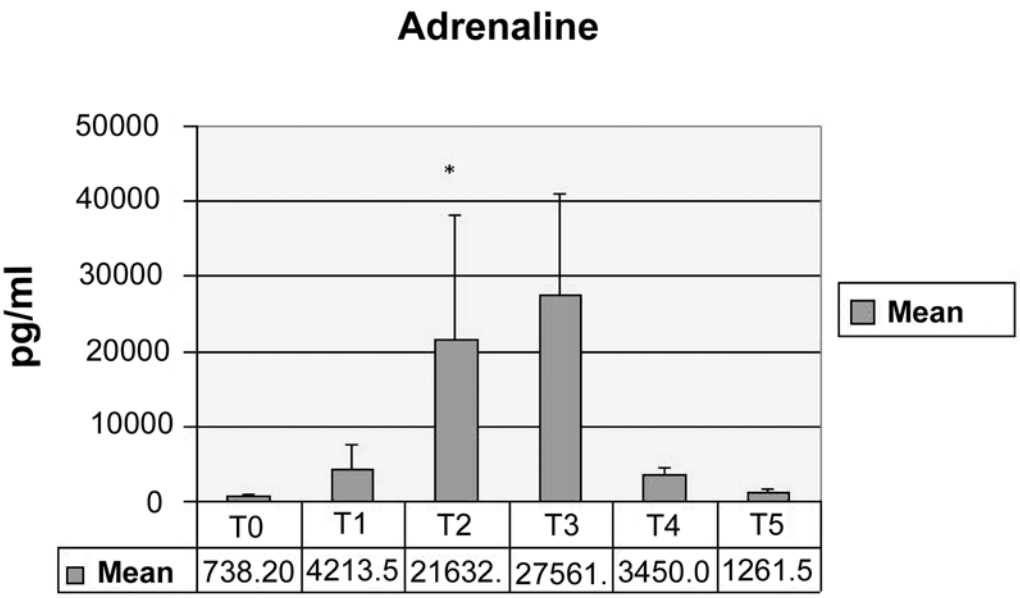
Following tumor ablation (T4), 5 hypertensive episodes were observed (Table-1).

Return to oral diet occurred between the first (D1) and the third (D3), with a mean of 1.9 days. Removal of the drain occurred between D2 and D3. Deambulation was authorized between D1 and D3 with a mean of 2.18 days. Discharge from hospital occurred between D3 and D6 with a mean hospital stay of 3.8 days. There was one damage to the adrenal vein, which was treated during surgery with no



** p < 0.01 comparing T2 to T0, ** p < 0.001 comparing T3 to T0 and T1, ***p < 0.01 comparing T4 to T2, **** p < 0.0001 comparing T5 to T3. T0: control before induction; T1: following the sequence induction-laryngoscopy-intubation; T2: during creation of pneumoperitoneum; T3: during manipulation-exeresis of pheochromocytoma; T4: following ablation of the pheochromocytoma; T5: in the recovery room following intervention when the patient is extubated and hemodynamically stable.*

Figure 1 – *Mean serum noradrenaline concentrations at different surgical times.*



** p < 0.01 comparing T2 to T0. T0: control before induction; T1: following the sequence induction-laryngoscopy-intubation; T2: during creation of pneumoperitoneum; T3: during manipulation-exeresis of pheochromocytoma; T4: following ablation of the pheochromocytoma; T5: in the recovery room following intervention when the patient is extubated and hemodynamically stable.*

Figure 2 – *Mean serum adrenaline concentration at different surgical times*

***Table 1** – Changes in blood pressure (BP) and heart rate (HR) during creation of pneumoperitoneum (T2), manipulation-exeresis (T3), ablation of pheochromocytoma (T4) and employed measurements.*

Patients / **Parameters**	**1**	**2**	**3**	**4**	**5**	**6 (Right Side)**	**6 (Left Side)**	**7**	**8**	**9**	**10**	**11**
BP (mmHg)	165/95	167/90	165/85	197/112	200/116	-	-	-	-	200/113	-	-
HR ($b.min^{-1}$)	-	110	-	140	-	-	-	-	-	118	-	-
Bolus nicardipine (mg)	6	6	4	4	4	-	-	-	-	6	-	-
Bolus esmolol (mg)	-	100	-	100	-	-	-	-	-	-	-	-
Bolus urapidil (mg)	-	-	-	50	-	-	-	-	-	-	-	-
BP (mmHg)	180/110	165/90	177/95	166/70	180/100	-	177/112	189/107	188/106	-	-	-
HR ($b.min^{-1}$)	120	110	-	-	-	-	-	-	-	-	-	-
Bolus nicardipine (mg)	4	4	6	4	4	-	-	3	2	-	-	-
Bolus esmolol (mg)	100	100	-	-	-	-	-	-	-	-	-	-
Bolus urapidil (mg)	-	-	-	-	-	-	25	-	-	-	-	-
Total dose of urapidil (mg)	70	60	40	100	60	125		40	40	60	50	40
BP (mmHg)	-	70/50	-	62/47	80/40	-	76/53	-	-	72/44	-	-
Bolus ephedrine (mg)	-	6	-	6	3	-	6	-	-	6	-	-

need for conversion to open surgery. This patient received transfusion of 2 units of red blood cells concentrate.

All patients were reassessed 6 months after intervention and presented normalized BP with no requirement for treatment.

COMMENTS

Laparoscopy effectively offers advantages for open surgery, that is less severe postoperative pain, early deambulation, reduced hospital stay and prompter return to daily activities (9,5). However, the surgery for management of pheochromocytoma differs from the approach used for other adrenal tumors due to the increased cardiovascular risks during the surgical intervention related to catecholamine release (2,10).

This study confirms that creation of pneumoperitoneum and tumor manipulation during videolaparoscopic ablation of pheochromocytoma are accompanied by a significant release of serum catecholamines. This release is probably responsible for hemodynamic disorders such as hypertensive peaks and sinus tachycardia.

Insufflation of pneumoperitoneum is associated with an increase in serum catecholamines, either by stimulus to mechanical compression or a change in tumor vascularization (11,12). Additionally, carbon dioxide used to insufflate the pneumoperitoneum can lead to hypercapnia, which would increase sympathetic tonus, thus changing tension levels (13).

In the cases evaluated in this study, the creation of the pneumoperitoneum produced an important release of noradrenaline into the blood stream, thus increasing its concentration when compared with preoperative values ($p < 0.01$). This release was variable and unpredictable between one patient and the other. In this series, pneumoperitoneum increased mean serum noradrenaline concentrations 12.7 times the baseline value and mean serum adrenaline concentrations increased 29.3 times the baseline value. These results are in agreement with the study by Joris et al. (7), who observed an increase in plasma catecholamine concentrations by 7 to 16 times the baseline value following the creation of pneumoperitoneum in patients with pheochromocytoma undergoing videolaparoscopic surgery.

Manipulation and ablation of the pheochromocytoma during laparoscopy equally produce an exaggerated release of serum catecholamines (14). In the series described in this study, manipulation and exeresis of pheochromocytoma (T3) evolved with high concentrations of serum noradrenaline and adrenaline. When assessing the mean concentrations of serum noradrenaline ($p < 0.001$) and adrenaline ($p < 0.01$), statistical differences were observed between T3 and pre-induction control (T0). In this series, despite early ligation of the adrenal vein, we observed an elevation in catecholamine concentrations during dissection of the adrenal gland.

According to some authors, tension variations are less important or equivalent during laparoscopy when compared to laparotomy (11). Joris et al. (15), studied hemodynamic changes relative to pneumoperitoneum with carbon dioxide in 20 healthy patients undergoing elective laparoscopic cholecystectomy. They also assessed the changes in several neurohumoral mediators, which can contribute to hemodynamic changes, such as plasma concentrations of cortisol, catecholamines, vasopressin, renin, endothelin and prostaglandins. Peritoneal insufflation resulted in significant reduction in cardiac output, as well as an increase in blood pressure and systemic and pulmonary vascular resistance. Laparoscopy resulted in a progressive and significant increase in plasma concentrations of cortisol, adrenaline, noradrenaline, renin and vasopressin. Prostaglandins and endothelins showed no significant change. The authors concluded that vasopressin and catecholamines probably measured the increase in systemic vascular resistance during insufflation of pneumoperitoneum with carbon dioxide.

Fernandez-Cruz et al. (10), reported that, in the case of pheochromocytomas, videolaparoscopic adrenalectomy is associated with a lesser increase in catecholamine levels in peripheral circulation when compared with laparotomy, and that hypertensive peaks are related to direct manipulation of the adrenal gland. The authors compared 23 videolaparoscopic adrenalectomies (non-functioning adenomas, aldosteroneproducing adenoma, Cushing's adenoma and Cushing's disease) using insufflation of pneumoperitoneum with carbon dioxide, with 8 videolaparoscopic adrenalectomies for pheochromocytoma using insufflation of pneumoperitoneum with helium, and with eight 8 adrenalectomies performed by the conventional open approach. They studied the serum changes in catecholamine levels and correlated them with intraoperative cardiovascular disorders in patients with pheochromocytoma. There was no significant difference between videolaparoscopic adrenalectomies due to pheochromocytoma compared to videolaparoscopic adrenalectomies due to other lesions, as regards surgical time, blood loss, hospital stay and return to usual activities. Results for these parameters were unfavorable to the open adrenalectomies group. A major increase in plasma catecholamine levels occurred in patients with pheochromocytoma during tumor manipulation in the videolaparoscopy group (17.4 times for adrenaline and 8.6 times for epinephrine) and in the open surgery group (34.2 times for adrenaline and 13.7 for noradrenaline). Cardiovascular instability was associated with open surgery only.

Among the studied cases, in 6 out of 12 adrenalectomies (50%), hypertensive peaks occurred during the creation of pneumoperitoneum (T2) and in 8 out of 12 adrenalectomies (66.6%), hypertensive peaks occurred during manipulation and exeresis of the gland. These hemodynamic changes occurred simultaneously with an increase in catecholamine levels during the creation of pneumoperitoneum and manipulation / exeresis of the gland.

Two independent predictive factors for perioperative morbidity are the secreting characteristic of the tumor, and its size (16). An excessive and unpredictable peroperative catecholamine release can lead to a serious clinic condition associated with malignant hypertension, mydriasis, pulmonary edema (17) and even acute heart failure (18).

Despite the association between the creation of pneumoperitoneum (T2) and manipulation (T3) of the adrenal gland with an increase in serum rates of noradrenaline and adrenaline, the adrenalectomies were performed with low morbidity. A laparoscopic exeresis of pheochromocytoma can be performed, but it requires proper preoperative preparation and careful perioperative anesthetic surveillance of blood pressure and occasional cardiac arrhythmias. The preoperative preparation is intended to decrease cardiovascular morbidity and includes alpha adrenergic blockade and, if required, beta adrenergic blockade. Hypertensive peaks in pheochromocytoma are related to the stimulation of alpha 1 receptors (19). In the series under study, preoperative control was achieved by previous blockade of alpha 1 receptors by prazosin and urapidil. Beta adrenergic blockade is not systematic and depends on the presence of associated tachycardia (19).

Two problems occur during pheochromocytoma surgery, and they require opposite solutions: 1) the catecholamine release during tumor manipulation leads to a risk of paroxysmal hypertension and episodes of sinus tachycardia, which can be effectively treated by associating nicardipine (calcium channel antagonist) and esmolol (selective beta blocker); 2) the significant decrease in catecholamine levels following tumor ablation can, contrarily, cause severe hypotension, which can be worsened by the persistent effects of alpha 1-antagonist drugs that have been introduced during preoperative preparation (19). Thus, the use of alpha 1-antagonists (Urapidil®) available for injection with short half-live and short action can be used during the preoperative period, offering a potential solution to both problems (20).

In a series with 8 patients, Joris et al. (7) used alpha 1-adrenergic blockers for preoperative preparation. During the intervention, they used an infusion of nicardipine (calcium channel blocker) for treating and preventing increases in blood pressure. Six of the 8 patients (75%) showed increased blood pressure higher than 25% of the baseline value during the creation of pneumoperitoneum. The authors reported that hemodynamic changes were easily treated through a continuous infusion of nicardipine associated with a beta blocker. The authors stated that no episode of acute hypotension (blood pressure lower than 60 mmHg) was observed in the 8 patients, probably because they had received vasodilators and/or were normotensive before surgery.

In the present series, during 12 adrenalectomies, 5 of the patients (41.6%) had hypotensive episodes and systolic blood pressure lower than 80 mmHg, and were treated by administering bolus ephedrine and volume reposition with crystalloids. However, no patient in this series presented pressure levels under 60 mmHg. Episodes of hypotension were related to the decrease in serum catecholamine concentrations observed after ablation of the gland. Serum noradrenaline concentrations, following adrenal ablation (T4), significantly decreased ($p < 0.01$) when compared with serum noradrenaline levels during creation of pneumoperitoneum (T2). When compared at T4 and T2, the decrease in serum adrenaline concentrations was not significant, probably due to the reduced number of study cases and the large variation in serum adrenaline concentration among the patients.

This study is in agreement with data from the literature, showing that videolaparoscopic adrenalectomy is feasible for management of pheochromocytomas and presents a low morbidity rate. The creation of pneumoperitoneum and the manipulation of the adrenal gland are related to an increase in serum catecholamines concentrations, and the ablation of the pheochromocytoma is related to a decrease in noradrenaline concentrations. In some cases, the changes in serum catecholamine concentrations correlate with hemodynamic disturbances, which, however, were easily treated.

CONCLUSION

The barotrauma promoted by installing the pneumoperitoneum with a pressure of 12 mmHg in patients with pheochromocytoma induced a significant increased in serum noradrenaline concentrations. In patients with pheochromocytoma undergoing videolaparoscopic adrenalectomy, surgical stress during manipulation of the adrenal gland promoted significant increases in serum concentrations of noradrenaline and adrenaline. The serum noradrenaline concentrations significantly decreased following ablation of the pheochromocytoma when compared with serum concentrations during creation of pneumoperitoneum and manipulation of adrenal gland.

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EDITORIAL COMMENT

The authors are to be congratulated for their excellent paper on laparoscopic surgery for pheochromocytoma but, in fact, the authors' overall conclusions were already expected.

Many papers concur that during adrenal manipulation (either laparoscopic or open), an increase in serum catecholamine usually occurs, with the possibility of hemodynamic events (1-5). As well, other papers have already shown the effects of pneumoperitoneum on the intra-abdominal vasculature - namely an increase in vascular resistance, a decrease in venous drainage and consequently, transient renal and liver dysfunction, intestinal congestion and increased serum catecholamine release. After desufflation, all parameters return to normal levels (6-10).

Unfortunately, there was no open adrenalectomy control group in order to compare the results.

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