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Plasmatic vasopressin in patients undergoing conventional infra-renal abdominal aorta aneurysm repair

Vasopressina plasmática em pacientes submetidos à correção de aneurisma de aorta infrarrenal

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Abstract

Objectives: **To evaluate plasmatic arginine vasopressin (AVP) levels in patients undergoing scheduled conventional abdominal aortic aneurysm (AAA) repair.**

Methods: **Plasmatic AVP concentrations were measured by radioimmunoassay in 22 non-consecutive adult patients undergoing infra-renal AAA repair. They were under combined general and epidural anesthesia at the following time frames: 1 - pre-operative (T0); 2 - 2h (T1) and 6h (T2) after the surgical procedure; 3 - in the morning at the first (T3), second (T4) and third (T5) post-operative days. Some clinical and laboratory variables were also recorded.**

Results: **The mean age of patients was 68±10 years; 17 were males. Plasmatic AVP (mean±SD; pg/mL) was within the normal range at T0 (1.4±0.7; baseline), increasing significantly at T1 (62.6±62.9; *P*<0.001) and at T2 (31.5±49.7; *P*<0.001), with a progressive fall, returning to basal levels at T5 (2.1±3.8; *P*=NS). Positive and statistically significant correlations were found between AVP and glycemia, serum lactate and white blood cells counts, but not with systemic arterial pressure or plasma osmolarity during the postoperative period.**

Conclusions: **Considering that no correlations were found between AVP levels and hemodynamic or plasmatic osmolarity variations in AAA repair, it seems that stress response is mainly secondary to noxious stimulation mediated by the autonomic nervous system that is not completely blocked by anesthetics.**

Descriptors: **Intensive care units. Cardiovascular abnormalities. Receptors, vasopressin.**

Resumo

Objetivos: **Avaliar os níveis plasmáticos de vasopressina (AVP) em pacientes submetidos à correção convencional de aneurisma de aorta abdominal (AAA).**

Métodos: **A AVP plasmática foi mensurada por radioimunoensaio em 22 pacientes não-consecutivos submetidos à correção eletiva de AAA infrarrenal sob anestesia geral + epidural nos seguintes momentos: pré-operatório (T0); 2h (T1) e 6h (T2) após a cirurgia; e nas manhãs do primeiro (T3), segundo (T4) e terceiro (T5) dia pós-operatório (PO). Variáveis clínicas e laboratoriais de interesse também foram anotadas.**

Resultados: **A média de idade dos pacientes foi de 68±10 anos, sendo 17 homens. A AVP plasmática (média±DP; pg/mL) estava dentro de limites normais no T0 (1,4±0,7; basal), aumentando no T1 (62,6±62,9; *P*<0,001) e no T2 (31,5±49,7; *P*<0,001), e retornando aos valores basais no T5 (2,1±3,8;**

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***P*=NS). Correlações positivas e significativas foram encontradas entre a AVP e glicemia, lactato sérico e leucócitos sanguíneos, mas não com a pressão arterial sistêmica ou com a osmolaridade plasmática no PO.**

***Conclusões:* Na cirurgia de reparação de AAA, considerando que nenhuma correlação foi encontrada entre os níveis de AVP e variações hemodinâmicas ou da osmolaridade plasmática, este achado sugere que a resposta ao estresse é predominantemente secundária aos estímulos dolorosos mediados pela parte autônoma do sistema nervoso, não completamente bloqueados pelos anestésicos.**

***Descritores:* Unidades de terapia intensiva. Anormalidades cardiovasculares. Receptores de vasopressina.**

INTRODUCTION

Stress response is the name given to a conjunction of hormonal and metabolic alterations occurring after trauma (accidental or surgical) or acute non-traumatic injuries encompassing a wide range of endocrinological, immunological and hematological effects [1].

Despite the knowledge that the stress response represents an evolving way to allow injured mammals to survive by metabolizing their body reserves, recently it has been discussed if this response is really necessary in current surgical practice. In this way, efforts have been made by many investigators to study these per-operative neurohormonal and metabolic alterations, as well as the influence of many different interventions (anesthetic, surgical and/or pharmacological) aiming to modify and/or to modulate them [2].

One of the stress response biomarkers of interest has been arginine vasopressin (AVP). In normal conditions, AVP is released into the systemic circulation by osmotic or by baroreflex stimulation secondary to hypovolemia or acute hypotension [2]. AVP release is also increased in many other clinical situations, such as nausea, pain, hypoxia, hypoglycemia and even smoking [2].

Increased plasmatic AVP has been reported after surgical procedures, especially those related to abdominal cavity [3], and after open-heart cardiopulmonary bypass surgery [4]. However, the subjacent mechanisms responsible for this response have not yet been fully clarified [5].

Therefore, AVP levels have been investigated as a physiological response to traumatic stress. Miltenberger and Moran [3] and Moran et al. [6] were pioneers in investigating the plasmatic AVP concentrations during surgical stress, reporting that upper abdominal visceral manipulation [3] and pain [6] could be potent stimuli to increase AVP release. Accordingly, Melville et al. [7] have suggested that painful impulses from the surgical site are the strongest stimuli for AVP releasing.

There are conflicting with data regarding the influence of blood pressure alterations during anesthetic/surgical procedures in plasmatic AVP. While some authors defend that acute hypotension can stimulate AVP release since arterial pressure drops are often seen during and after anesthetic/surgical procedures [8], others disagree as they had not found a significant correlation between plasma AVP concentrations and arterial pressure levels at different times of surgical procedures [9]. So, despite the well documented plasmatic AVP increase during major surgical procedures, the subjacent mechanisms responsible for this exceptional AVP releasing to remain incompletely understood [5,10].

Conventional surgical abdominal aortic aneurysm repair (CAAAR) is one of the most stressful surgical procedures known, carrying a high rate of early morbidity and mortality, greater than that reported during minimally invasive procedures, such as endovascular ones [11]. However, there are few reports in medical literature evaluating the stress response by measuring serial AVP concentration during postoperative for periods longer than 24h after CAAAR [12-15]. Thus, the main objective of the present study was to prospectively evaluate the time course of plasma AVP concentrations in patients undergoing conventional infra-renal AAA repair during the first 72 postoperative hours.

METHODS

Study design and setting

A prospective observational study was performed in patients scheduled for CAAAR at the Hospital de Clínicas from University of Campinas (UNICAMP), São Paulo, Brazil. The study protocol was approved by our Institutional Review Board (protocol Nº 383/2004) and a written informed consent was obtained from the patients or their surrogates at the preoperative period.

Patients

Between October 2004 and March 2005, 25 non-consecutive adult patients, scheduled for CAAAR were initially selected for inclusion in this investigation. From those, 22 patients completed the protocol, composing the final study population. The indication for correction of AAA (considering diameter) was:

- AAA > 5.5 cm and growth rate per year > 1.0 cm [16];
- Currently, the indication for correction of AAA is: > 5.5 cm or growth rate > 0.7 in six months or > 1.0 cm in one year [17].

Three patients were excluded due to cancellation of previously scheduled surgery.

Preoperative exclusion criteria were: age < 18 years; urgency/emergency surgical procedures; patients with signs and/or symptoms suggestive of infection/sepsis; recent myocardial infarction or stroke (less than one month); heart failure NYHA class III or IV; or patient's refusal to give informed consent. Postoperative exclusion criteria were: mechanical ventilation longer than 24 hours; re-operation for any cause during the observation period; circulatory shock; impossibility to get all blood samples for laboratory tests as scheduled, either by the technical difficulties or the patient's refusal; death by any cause in a time ≤ 72 hours after surgery; and patient's refusal to remain in the study protocol at any time.

Anesthetic and surgical procedures

All patients were anaesthetized by the same medical team during the inclusion period. Combined epidural (with bupivacaine 0.25%) and general intravenous and inhalation anesthesia were used. The patients were pre-medicated with midazolam (0.08 to 0.1 mg/kg). Before anesthetic induction, a double central venous catheter (Arrow, 7F) was percutaneously inserted via the internal jugular vein. An arterial line was also obtained for continuous arterial pressure monitoring. Anesthesia induction was done with sufentanil (1-2 mg/kg) or alfentanil (30-50 mg/kg), followed by a hypnotic agent either midazolam (0.05-0.2 mg/kg), or etomidate (0.3 mg/kg) or propofol (1.0-2.5 mg/kg), and a neuromuscular blocking agent, either vecuronium (0.1-0.2 mg/kg), or rocuronium (0.6-1.0 mg/kg) or pancuronium (0.08-0.1 mg/kg), at the discretion of the anesthetic team. Soon after, the patients were orotracheally intubated and a bladder catheter was inserted. In the vaporizer equipment it was used an isoflurane (0.5%-1.0%) mixture with oxygen-air.

Every patient has undergone midline abdominal wall incisions with standard exposure of the aorta that was cross-clamped just below the crossing of the left renal vein. During aortic cross-clamping sodium nitroprusside was administered to patients who became hypertensive. After aortic declamping, isotonic crystalloid solutions were administered, as well as dopamine or norepinephrine, at the discretion of the anesthetic and/or surgical team, to keep mean arterial pressure between 80-100 mmHg.

After the end of surgery, all patients were admitted to the surgical intensive care unit. Postoperative care was conducted at the discretion of ICU team, without any interference of the main investigators.

Scheduled times for clinical and laboratory collecting samples and measurements

The following schedule was set to record selected clinical variables and to concomitantly collect venous blood samples for laboratory analysis and plasmatic AVP determinations: preoperative (T0); 2h postoperative (T1); 6h postoperative (T2) and in the morning of the first (T3), second (T4) and third postoperative day (T5).

Clinical and laboratory data recorded at postoperative period

During the postoperative period, the following clinical and laboratory data were recorded at all scheduled times: mean arterial pressure (MAP), heart rate (HR), hematocrit, serum lactate, serum sodium, serum potassium, glycemia. Plasma osmolarity was calculated. Urinary output was recorded from the first to the third post-operative day. White blood cells and platelets counts were done at first, second and third postoperative day. Serum creatinine was measured at the second and third postoperative day.

Methods for hormonal determination

For AVP determination blood samples were immediately centrifuged at 4ºC and the plasmatic fraction was stored at -80ºC. AVP concentration was measured by radioimmunoassay (RIA) after extraction of plasma (1 mL) with acetone and petroleum ether, at the Laboratory of Endocrine Physiology, Ribeirão Preto School of Medicine, University of São Paulo, as previously reported [18]. The percentage of recovery after extraction was 83% (ranging from 50% to 99%). AVP antiserum was purchased from Peninsula Laboratories Inc. (Belmont, CA) and ^{125}I-AVP from Dupont (Dupont NEN Research Products, Boston, MA). The assay sensitivity and intra- and inter-assay coefficients of variation for AVP were 0.14 pg/mL, 7.4% and 16.8%, respectively. All samples from an individual subject for AVP tests were determined in duplicate in the same assay.

Statistical analysis

The SAS System software for Windows (Version 8.02; SAS Institute Inc, 1999-2001, Cary, NC, USA) was used. ANOVA (Analysis of Variance for Repeated Measures) was used to evaluate the course of clinical and laboratory variables (including plasmatic AVP) over time. The profile contrast test was used for comparison between times. Since there was no normal distribution, variables were transformed into ranks or posts. Spearman's correlation coefficient was used to analyze the relationship between numerical variables. Differences were considered statistically significant when $P < 0.05$.

RESULTS

The final population of the present study was composed by 22 patients (17 males and five females). Fifteen patients received aortic-bi-iliac grafts and seven aortic-aortic grafts. Their basal characteristics are shown in Table 1.

The patients had a median age of 70 years, with predominant ASA 3 score (82%) and classification Goldman

Table 1. Basal characteristics of the study population (n = 22)

Variable	Mean (SD)	Median (Range)
Age (years)	68.2 (10.2)	70 (49-82)
Weight (kg)	71.2 (12.5)	68.5 (52-94)
Height (cm)	166 (9)	168 (151-185)
Body mass index (kg/m^2)	26 (5)	25 (17-41)
Comorbidities	Yes	%
Diabetes Mellitus type II	7/22	32
Systemic Arterial Hypertension	20/22	91
Chronic Coronary Artery Disease	9/22	41
Previous Myocardial Revascularization	3/22	14
Preoperative risk scores	N	%
ASA score 1/2/3/4/5/6	0/3/18/1/0/0	0/14/82/4/0/0
Goldman Classification I/II/III/IV	4/16/2/0	18/73/9/0

ASA – American Society of Anesthesiologists

2 (73%). The prevalent co-morbidities were hypertension (91%), chronic coronary artery disease (41%) and type-II diabetes mellitus (32%). Only three (14%) patients had been previously undergone coronary artery bypass grafting.

Mean surgical time was 4.3±1.1 hours (median = 4.0 hours; range = 3–8 hours). Estimated blood loss was 1,120 ± 475 mL (median = 1,000 mL; range = 400-2,000 mL). Packed red cells (PRBC) were administered to 15/22 (68%) patients, but only four (18%) patients received more than two units, and none received more than five units. No life threatening hemodynamic disorder was documented during surgery.

Clinical and laboratory variables' values recorded at different observation times are shown in Table 2. They were compared to preoperative (T0) data.

Decreasing in MAP was seen during the first 24

Table 2. Clinical and laboratory variables, expressed as mean (± SD) [Range], recorded at diferente observation times (n = 22)

Variable	Pre-OP	2h-PO	6h-PO	1st day PO	2nd day PO	3rd day PO	==-value
MAP	97 (12)	87(15)*	86 (11)*	87 (17)*	100 (21)	102(12)*	(*) <0.001
(mmHg)	[70-117]	[59-113]	[66-117]	[47-118]	[51-127]	[78-120]	
HR	69 (11)	88 (17)*	88 (22)*	88 (15)*	92 (14)*	88(13)*	(*) <0.001
(bmp)	[48-84]	[52-121]	[56-130]	[67-127]	[72-126]	[66-116]	
Urine output	—	—	—	130 (97)	123 (51)	—	0.678
(mL/h)				[50-536]	[58-281]		
Lactate	15 (0.5)	2.2 (1.4)*	2.2 (1.4)*	1.9 (0.9)	1.4 (0.6)	1.3 (0.5)	(*) <0.001
(mMol/L)	[0.9-2.9]	[0.9-7,5]	[0.8-6.4)	[0.7-4.0]	[0.8-2.7]	[0.5-2.6]	
Glycaemia	130 (48)	145 (38)	177 (58)*	158 (37)*	142 (51)	141 (60)	(*) <0.001
(mg/dL)	[83-288]	[84-218]	[108-307]	[88-229]	[92-293]	[76-355]	
Urea	42 (17)	—	—	—	—	36 (17)*	(*) <0.003
(mg/dL)	[11-81]					[16-77]	
Creatinine	12 (0.4)	—	—	—	—	1.0 (0.4)*	(*) <0.002
(mg/dL)	[0.6-23]					[0.5-2.1]	
Sodium	136 (2.6)	135 (3.8)	134 (3.6)	134 (3.2)	134 (3.1)	134 (3.1)	0.081
(mEq/L)	[132-140]	[128-146]	[128-141]	[128-140]	[128-140]	[127-139]	
Potassium	40 (0.5)	4.3 (0.6)*	4.2 (0.6)	4.3 (0.6)*	3.9 (0.5)	3.9 (0.4)	(*) <0.001
(mEq/L)	[3.2-50]	[3.4-5.6]	[3.1-5.5]	[3.1-5.7]	[3.1-5.3]	[3.0-4.6]	
OsmSer	279 (5)	278 (5)	279 (6)	277 (7)	277 (6)	277(6)	0.256
(mOsm/L)	[270-288]	[268-288]	[269-289]	[263-287]	[264-287]	[266-286]	
Haematocrit	42 (5)	—	—	33 (6)*	31 (4)*	30(3)*	(*) <0.001
(%)	[31-49]			[26-46]	[23-40]	[24-39]	
WBC	8.2 (1.9)	—	—	13.9 (4.1)*	11.7 (3.3)*	9.3 (3.5)	(*) <0.001
(mmm^3) x 10^2	[4.6-12.3]			[6.6-21.5]	[6.8-21 5]	[4.1-17.8]	
Platelets	224 (78)	—	—	167 (67)*	145 (59)*	160 (62)*	(*) <0.001
(mmm^3) x 10^2	[118-394]			[59-3 22]	[75-286]	[91-288]	
AVP	1.4 (0.7)	62.6 (62.9)*	31.5 (49.7)*	4.4 (4.3)*	2.1 (1.4)*	2.1 [3.8]	(*) <0.001
(pg/mL)	[0.3-3.1]	[4.2-250.0]	[1.4-205]	[1.1-20 5]	[0.15-5.0]	[0.15-19.0]	

AVP – Angine-vasopres sin; HR – Heart rate; MAP – Mean Arterial Pressure; OsmSer – Serum osmolarity (calculated); PO – Postoperative; Pre-OP - preoperative period (control); WBC – white blood cells. (*) Statistically significant differences in relation to preoperative (control) values

postoperative hours (at T1, T2 and T3), with subsequently normalization (at T4) and a slight tendency to increase above basal values at T5. Heart rate remained elevated from T1 to T5.

Serum sodium and calculated plasma osmolarity did not change significantly during the observation period. Serum potassium has shown a bimodal variation, increasing during the first postoperative hours, with subsequent normalization and decreasing at T5. Postoperative renal dysfunction was not observed.

Hematocrit decreasing (at T3, T4 and T5), white blood cells increasing (at T3 and T4) and platelets decreasing (at T3, T4 and T5) were observed.

Serum lactate increasing was observed at T1 and T2. Glycemia has also shown a significant increase during the first 24 postoperative hours (at T1, T2 and T3), subsequently returning to preoperative values.

Plasmatic AVP levels increased at the first six post-operative hours (T1 and T2), decreasing thereafter, but remaining above basal values until T4. Plasmatic AVP time course is shown in Figure 1.

The correlations between selected numerical variables and plasma AVP levels at each scheduled time are shown in Figures 2 and 3. No significant correlations were found between AVP and MAP and plasma osmolarity at any time. At T2, positive correlations were observed between AVP and serum lactate (r = 0.60; *P* = 0.003) and glycemia (r = 0.45; *P* = 0.04). At T3 there was a persistent positive correlation between AVP and serum lactate (*P* = 0.60; r = 0.003), and a positive correlation was also observed between AVP levels and white blood cells count (r = 0.58; *P* = 0.004). No significant correlations were found between plasma AVP levels and the respective selected variables at T0, T4 and T5.

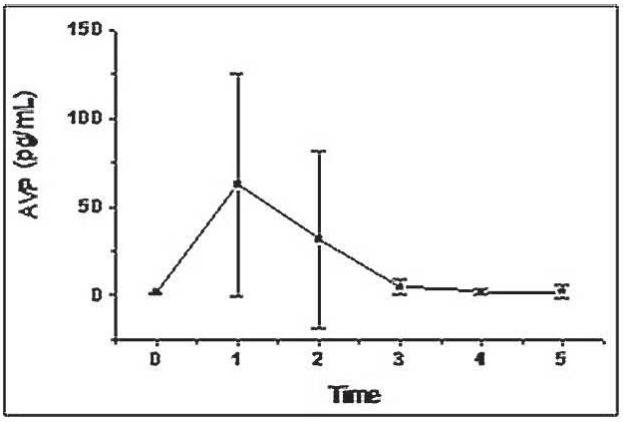

Fig. 1 – Plasmatic vasopressin concentrations
Plasmatic vasopressin concentrations (AVP – pg/mL; mean ± SD) at different observation moments (n = 22).
*T0 = pre-operative (control); T1 = 2h-PO; T2 = 6h-PO; T3 = 1st PO day; T4 = 2nd PO day; T5 = 3rd PO day (*P < 0.001 in relation to pre-operative period).*
PO = postoperative

DISCUSSION

The abdominal aorta aneurysm (AAA) incidence has been increasing due to population ageing [19]. In the present investigation, although composed by a convenience sample, the included patients have shown demographic characteristics similar to those reported in the literature for the AAA, i.e., there was a prevalence of older people (> 65 years old) and males (77%) [19]. Regarding expected co-morbidities for this population, the

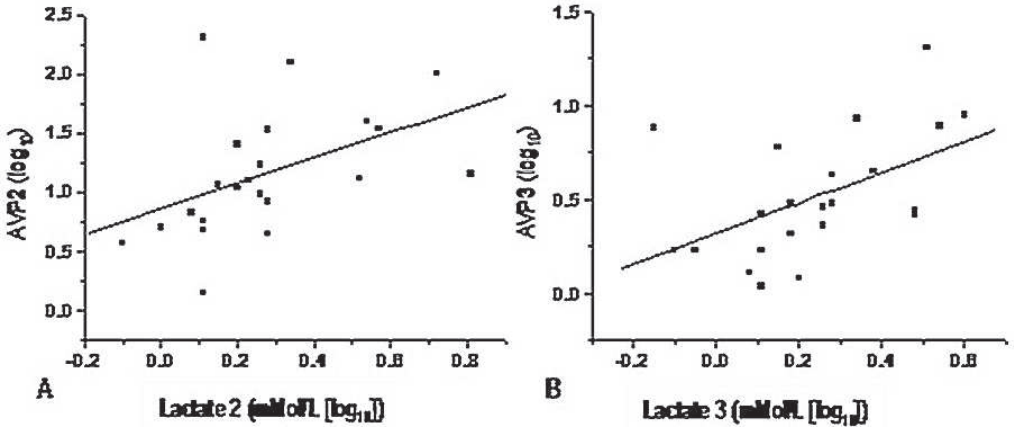

Fig. 2 – Correlations between plasmatic arginine-vasopressin and serum lactate.
A. AVP2 (pg/mL [log10]) and Lactate2 (mMol/L[log10]) at T2 (6h-PO) (r = 0.60; P = 0.003).
B. AVP3 (pg/mL [log10]) and Lactate3 (mMol/L[log10]) at T3 (24h-PO) (r = 0.45; P = 0.04).
AVP = arginine vasopressin

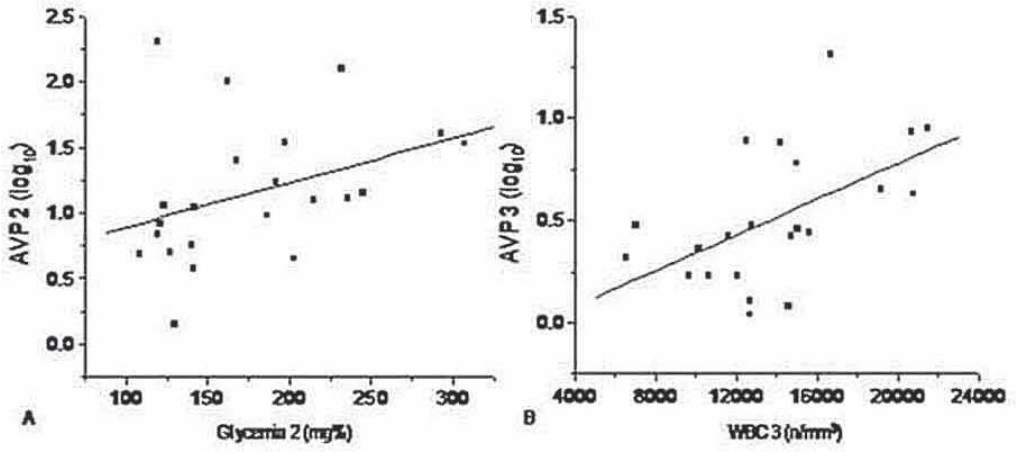

Fig. 3 – Correlation between plasmatic arginine-vasopressin, gkycemia and white blood cells.
A. Correlation between plasmatic arginine-vasopressin (AVP2; pg/mL [log_{10}]) and glycemia (Glycemia2; mg%) at T2 (6h-PO) (r = 0.45; P = 0.04).
B. Correlation between plasmatic arginine-vasopressin (AVP3; pg/mL[log_{10}]) and white blood cells (WBC3; n/mm³) at T3 (24h-PO) (r = 0.58; P = 0.004)

data were also in accordance with literature reports [19,20].

The majority of the patients have been classified as moderate risk for per-operative cardiac complications, as expected by their main disease and co-morbidities [11,20]. Patients showed a moderate surgical risk, and they have been in accordance with the estimated cardiac risk obtained by applying the Goldman scale.

Time course of vasopressin in our patients

AVP plasma levels in healthy, humans adults at restare usually very low. Chen et al. [21] reported plasma AVP levels varying from 2.2 to 8.0 pg/mL in normovolemic patients and normotensive patients, with serum osmolarity ≤ 290 mOsm/L. In a previous study of our group [22], plasma AVP values in 29 healthy adults individuals at rest were also very low (ranging from 0.4 to 5.2 pg/mL).=

In the present investigation, preoperative (T0 – basal period) mean plasma AVP levels were of 1.37±0.73 pg/mL (median=1.34 pg/mL; range=0.30 – 3.1 pg/mL), thus, inside those previously described by our group [22] in healthy resting adult individuals.

In the postoperative period there was an expressive and statistically significant increase in plasmatic AVP levels in the studied population, peaking at T2 (2h-PO; 62.6±62.9 pg/mL; $P < 0.001$), followed by an exponential drop during the first 24 post-operative hours, remaining still showing important variations thereafter, but just no more statistically differing from basal values at T5 (72h-PO; 2.12 ± 3.82 pg/mL; *P*=NS).

This time course of plasmatic AVP concentrations in patients undergoing general surgical procedures has been reported since the first half of the 1960s [3,6], and their greatest levels has been observed in those patients undergoing heart surgeries, with [4] or without cardiopulmonary bypass [5]. Increasing in plasma AVP levels usually begin just after surgical skin incision, peaking during the intra-operative period [3,23] or just after the first postoperative hours [6], followed by an exponential drop during the first 24 postoperative hours in uncomplicated patients [23].

In the present study, plasmatic AVP was not measured during the intra-operative period, but its time course pattern at the postoperative period has been similar to those reported by many authors in different major general surgical procedures, as discussed previously, peaking early (T1–2h-PO), then exponentially dropping during the first 24 postoperative hours, tending to normalize thereafter.

The pathophysiologic mechanisms responsible for this dramatic increase in plasma AVP in the per-operative period of major scheduled surgical procedures had not yet been fully clarified [5,24], but it can be influenced by the type [4,5,7,8,10] and invasiveness [25] of the surgical procedure, the type of employed anesthesia [24,26], and by hemodynamic [8,27] and/or serum osmolarity alterations in the per-operative period [24].

Concerning scheduled surgical AAA repair, there are only few studies in the literature that have specifically evaluated plasma AVP concentrations time course as a marker of surgical stress response during the first 72 postoperative hours.

In this research line, Kataja et al. [12], in 1989, evaluated hormonal and cardiovascular responses after aortic cross-clamping and declamping in 20 patients undergoing conventional surgical AAA repair. The patients were divided

into two groups: 10 control patients and 10 patients, which have been medicated with the oral captopril (25 mg), one day and one hour before surgery, in aim to prevent hypertension during the intra- and postoperative period. After anesthetic induction, in the group treated with captopril hypotension was observed in four patients and bradycardia in three of them. In the postoperative period, patients of both groups have presented hypotension and tachycardia. Furthermore, in both groups, plasmatic AVP levels have increased significantly before aortic cross-clamping and during the post-operative period.

Lasson et al. [14], in 1995, have investigated AVP releasing in 30 patients undergoing conventional infra-renal AAA surgical repair, which has been divided into two groups: group I (n=15), patients receiving dopamine 3 µg/kg/min intra-operatively and during the first 24 postoperative hours, and group II (n=15), patients who received placebo at the same respective times, documenting an increase in plasma AVP in the dopamine treated group. Due to this unexpected finding, the authors have suggested that the greater incidence of nauseas during the postoperative period in patients treated with dopamine could be the cause of this greater plasma AVP increasing.

Kruimel et al. [28], in 1999, evaluated the relationship between immune and neuroendocrine responses in 18 patients undergoing conventional scheduled AAA repair (aneurysmatic and atherosclerotic obstruction), at pre-, intra- and postoperative periods. Plasma levels of cytokines, AVP, ACTH, and cortisol was serially measured. AVP and ACTH plasma levels have significantly increased during the intra-operative period, but cortisol levels did not change. The authors have also demonstrated a depression in circulating levels of IL-1β (pro-inflammatory) and an increase of IL-1ra (anti-inflammatory) levels during surgical stress. The *ex-vivo* production of IL-1β and TNF-á was suppressed, indicating a depression in the production of these cytokines. These findings have been a parallel behavior compared to that of hormonal stress response expressed by the elevated levels of plasma AVP and ACTH, but not to that of cortisol, suggesting that glucocorticoids are not a key-factor for the depression in the production and releasing of pro-inflammatory cytokines.

In order to reduce the surgical stress response, a variety of less invasive techniques have been developed in the last years. Minimally invasive surgical procedures have permitted minor incisions and lesser manipulation during tissue dissection, resulting in a reduction of per-operative physiological disturbances. Thus, endovascular AAA repair, a minimally invasive technique, has been defended as an alternative to conventional surgical one [29].

In this way, in 2007, Kataja et al. [15] investigated the postoperative metabolic response by comparing conventional and endovascular AAA repair under different anesthetic patterns, and concluded that the endovascular approach under spinal anesthesia has induced lesser physiologic disturbances when compared to conventional (open) approach under general anesthesia with the epidural blockade. AVP plasmatic levels were significantly higher during conventional open AAA repair just after aortic declamping and at the postoperative period when compared to the group undergoing endovascular approach. However, with both techniques, an increase in plasmatic AVP levels was observed when compared to pre-anesthetic values.

Correlations between plasmatic AVP and some selected variables

In the present study, no correlations were found between plasma AVP levels and MAP or plasma osmolarity (calculated) variations, known as the most important stimulus for the regulation of AVP secretion and release [2]. Similar findings have been previously reported by other authors in different surgical procedures [24].

These findings lead us to conclude, in accordance with other authors' statement, that, in intra-abdominal surgeries (as in the case of conventional AAA repair), noxious stimulus, probably mediated by the autonomic nervous system, are, really, the most important factors for AVP increased releasing [6,7,10].

Other interesting findings in our study include the powerless but otherwise positive and statistically significant correlations, found between plasmatic AVP and blood glucose at T2 (6h-PO) and serum lactate at T2 (6h-PO) and at T3 (24h-PO). These factors strongly ratify the role of AVP as a biomarker of surgical stress response intensity, since these alterations are ubiquitously seen as components of normal metabolic response to trauma [1].

An additional relevant finding was the positive and significant correlation found between plasma AVP and white blood cells count at T3 (24h-PO), suggesting that the greater the surgical stress, expressed by the amount of AVP releasing, the greater the possibility of the patient to develop a postoperative systemic inflammatory response syndrome (SIRS). In this way, the circulating levels of AVP could be a useful marker to prognosticate postoperative inflammatory complications. However, due to many technical difficulties (the need for refrigerated blood sample's centrifugation and to store them at -80ºC to avoid the fast hormone degradation by plasma vasopressinases, associated to need of employ radioimmunoassay techniques for its measurement and the possibility of pre-analytical errors), the routinely measurement of AVP is, unhappily, not feasible [30].

Recently, copeptin, a 39-amino acid glycopeptide that comprises the C-terminal part of the AVP precursor (CT-proAVP), was found to be a stable and sensitive surrogate marker for AVP release, analogous to C-peptide for insulin. The great advantage is that copeptin is very stable in

plasma samples and can be measured by immunoluminometric assay, thus turning it into a useful and indicative surrogate of plasmatic AVP levels, with the additional advantage that its measurement is feasible in daily clinical practice [30,31]. Thus, the copeptin evaluation of time course could bring additional and valuable data to better understanding the role of vasopressin in the pathophysiology of surgical stress response.

Limitations of the present study

The present study has many limitations, and some of them must be highlighted. *First*, it was a descriptive, non-comparative study, with a small convenience sample, and thus composed by a heterogeneous population. *Second*, the anesthetic techniques were not standardized, since they remain at the discretion of the anesthesia team, and this, certainly had been important, but impossible to measure, influence on the stress response. *Third*, the types of corrective AAA surgery also have varied (prosthesis aortic-aortic, aortic-bi-iliac, etc), and this could have increased the manipulation degree as long as the surgical time, factors well known as modifiers of stress response. *Fourth*, hemodynamic and laboratory variables were not recorded during intra-operative period, as long as plasma AVP levels, so we could not be sure to which moment AVP levels have really peaked. *Fifth*, plasma osmolarity was calculated and not directly measured, and this could not have reflected the real patients' conditions. *Sixth*, post-operative care was done at the discretion of ICU team, and important factors well known to have been significant influence upon AVP releases were not controlled, such as: the type and pattern of fluid administration, the type and level of sedation and analgesia employed, type and doses of vasoactive drugs, diuretic use etc. Finally, we analyzed only the white blood cells count as a surrogate sign of SIRS. We are conscious that a concomitant measurement of other inflammatory biomarkers, such as tumor necrosis factor-alpha, interleukins, C-reactive protein, procalcitonin, etc., could certainly have enriched our analysis of post-operative stress response, thus helping to clarify the role of plasma AVP level as a prognostic factor of post-traumatic SIRS.

CONCLUSION

The time course of AVP plasmatic levels in patients undergoing scheduled conventional non-complicated correction of the infra-renal abdominal aorta aneurysm has shown the same pattern reported in many different types of surgical procedures in the literature, peaking at the first post-operative hours with a subsequent exponential drop, returning to basal (pre-operative) levels 72 hours (3rd post-operative day) after the surgical procedure. Considering that no correlations were found between AVP levels and hemodynamic or plasmatic osmolarity variations, it seems this stress response is mainly secondary to noxious stimulation mediated by the autonomic nervous system, which is not completely blocked by anesthetics. The clinical implications of this AVP response pattern during major surgical procedures, either on the cardiovascular, metabolic and inflammatory postoperative outcome, remain to be further investigated.

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