The effect of the maze procedure on the secretion of arginine-vasopressin and aldosterone

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Background: Excessive fluid retention is a serious complication after the maze procedure that cannot be totally explained by changes in levels of atrial natriuretic peptide. We therefore measured circulating levels of arginine vasopressin and aldosterone in patients undergoing the maze procedure to study their possible role in this postoperative complication.

Methods: Serial arginine vasopressin and aldosterone levels were monitored for 72 hours in 11 patients after coronary artery bypass grafting and in 13 patients after the maze procedure. Hemodynamic data, urine output, fluid balance, and complications were recorded prospectively during the same period of time.

Results: Plasma levels of arginine vasopressin and aldosterone were significantly higher in patients after the maze procedure when compared with patients after coronary artery bypass grafting.

Conclusions: This study documents that the maze procedure results in increased plasma arginine vasopressin and aldosterone levels and indicates that they, rather than atrial natriuretic peptide alone, participate in the excessive postoperative fluid retention that follows the maze procedure. We believe that these hormone elevations are most likely secondary to a temporary lack of response of the atrial baroreceptors. These results may explain the effectiveness of spironolactone therapy after the maze procedure.

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The maze procedure has been demonstrated to be a safe and effective surgical therapy for medically refractory atrial fibrillation.¹⁻³ One of the earliest recognized postoperative complications of the maze procedure is excessive fluid retention, with a reported incidence of 12% to 36%.^{4,5} In its most severe form, fluid retention may result in pulmonary edema and symptomatic pleural effusion in the immediate postoperative period.

The cause of this postoperative abnormal fluid imbalance remains uncertain. Several authors have suggested that a significant decrease in the secretion of atrial natriuretic peptide (ANP) postoperatively may play a role in the excess fluid retention. This hypothesis suggests that the decreased ANP levels after the maze procedure result from the multiple atriotomy incisions and excision of both atrial appendages rather than from the conversion of atrial fibrillation to normal sinus rhythm.⁶⁻⁸ However, a significant reduction in ANP levels has also been observed in patients after external cardioversion for chronic atrial fibrillation, which is generally not associated with fluid retention.⁹ Taken together, these findings indicate that the ANP level is not the only determinant of postoperative fluid retention seen after the maze procedure.

Arginine vasopressin (AVP) is released into the systemic circulation in response to an increased plasma osmolality or as a reflex response to decreases in blood volume- or blood pressure-sensed baroreceptors in the atria and pulmonary arteries.¹⁰⁻¹⁸ Many of the cardiovascular and renal effects of AVP, and its stimulus for secretion, are antagonized by ANP.¹¹ At the level of the hypothalamo-neurohypophyseal axis, high concentrations of ANP can inhibit AVP secretion and adrenocorticotrophic hormone release. ANP also inhibits steroidogenesis, especially mineralocorticoid synthesis, in the adrenal cortex. The endocrine effects of ANP therefore complement its cardiovascular and renal effects by antagonizing the sodium and water retention caused by aldosterone and AVP, respectively.¹²

We propose that the temporary loss of atrial stretch receptors and possibly the decreased level of ANP after the maze procedure result in a relative increase in AVP and aldosterone levels. Elevated serum AVP and aldosterone, in addition to ANP deficiency, thus participate in causing the immediate postoperative fluid retention observed in patients undergoing the maze procedure.

Methods

This study (1) examines serial changes in AVP levels after the maze procedure and compares them with those after non-maze heart surgery and (2) determines whether serum aldosterone levels correlate with AVP changes in the same set of patients.

Patients

After the study was approved by the Georgetown University Investigative Review Board and informed consent was obtained, 24 patients were enrolled. The subjects were divided into 2 groups: group I, patients tested after the maze procedure ($n = 13$), and group II, patients tested after coronary artery bypass grafting (CABG) ($n = 11$). All patients underwent operation for the first time and were admitted for surgery electively. Patients with renal failure (serum creatinine ≥ 1.5 mg/dL) and patients receiving preoperative treatment with diuretics or angiotensin-converting enzyme inhibitors were excluded from the study.

Blood Samples

Blood samples were taken at 5 different time points from patients in both groups. A baseline sample was taken in the operating room before any anesthesia. Four samples were then taken postoperatively beginning at 6 hours and then at 24, 48, and 72 hours postoperatively.

All samples were drawn into 10-mL heparinized tubes and centrifuged immediately for 10 minutes at 4°C. The plasma was separated and stored at -70°C until the assay for AVP, aldosterone, and ANP levels was performed. Each blood sample was coded and numbered so the laboratory work could be performed without knowing the patient's name, type of disease, or surgical procedure.

AVP Radioimmunoassay

The plasma samples were thawed and extracted using the acetone-ether method. Briefly, 1 mL of acetone (Fisher Chemicals, Fair

Lawn, NJ) was added to 0.5 mL of plasma and centrifuged for 20 minutes at 2600 rpm. The supernatant was removed, and 1 mL of anhydrous ethyl ether (Merck KGaA, Darmstadt, Germany) was added. This was allowed to settle for 30 minutes. The upper ether phase was discarded. The remaining sample was dried with a vacuum centrifuge and then reconstituted in 250 μ L of assay buffer (0.01 mol/L K_2HPO_4 , 1.5 mol/L NaCl, and 0.25% bovine serum albumin, pH 7.4). The radioimmunoassay (RIA) was performed by incubating 100 μ L of plasma extract or a known amount of AVP standards (0.01-50 pg per tube, Peninsula Laboratories, Belmont, Calif) with 100 μ L of anti-AVP antibody and 200 μ L of assay buffer for 24 hours at 0°C to 4°C. Then, 100 μ L of ^{125}I -AVP tracer (~ 3200 cpm, NEN Life Science Products, Boston, Mass) was added and continuously incubated for 3 to 4 days at 0°C to 4°C. Incubation was stopped by the addition of 50 μ L of 0.03% gamma globulin (Amersham Life Science, Arlington, Ill) and 1 mL of 25% PEG 8000 (Fisher). Free ligand was decanted. The residue was counted for 1 minute using a Gamma Counter (Titertek Instruments, Huntsville, Ala). The standard curve and plasma AVP concentration were calculated with RIA software AGC 2 (Titertek Instruments).

Aldosterone Radioimmunoassay

Plasma aldosterone levels were measured using the Coat-A-Count aldosterone RIA kit from the Diagnostic Products Corporation (Los Angeles, Calif). Briefly, 200 μ L of plasma and 1.0 mL ^{125}I -aldosterone were added to polypropylene tubes coated with an aldosterone-specific antibody. The mixture was incubated at room temperature for 18 hours. The tubes were decanted thoroughly. The residue was counted for 1 minute using a Gamma Counter. The standard curve and plasma aldosterone concentrations were calculated with RIA software AGC 2.

Atrial Natriuretic Peptide Radioimmunoassay

Plasma ANP levels were measured using the ANP RIA kit from American Laboratory Products (Windham, NH). The plasma samples were thawed and purified using a SepPak C18 cartridge (Waters, Milford, Mass). The cartridges were pretreated with 5 mL of 4% acetic acid in 86% ethanol followed by 5 mL of methanol and 5 mL of distilled water; 0.5 mL of plasma was acidified with 1.5 mL of 4% acetic acid and applied to the cartridge. The cartridge was rinsed with 3 mL of distilled water, and then ANP was eluted with 3 mL of acetic acid in 86% ethanol. The samples were evaporated under a light stream of nitrogen gas and then reconstituted in 250 μ L of assay buffer (0.2 mol/L borate and 0.2% bovine serum albumin, pH 8.4). The RIA was performed by incubating 100 μ L of plasma extract or known amount of standards (0.78-100 pg ANP) with 200 μ L anti-ANP antibody and ^{125}I -ANP tracer overnight at 0°C to 4°C. Free ligand was decanted thoroughly. The residue was counted for 1 minute using a Gamma Counter. The standard curve and plasma ANP concentration were calculated with RIA software AGC 2.

Parameters Checked

The following parameters were assessed for potential interactions with plasma AVP and aldosterone levels: age, gender, left ventricular function, blood pressure (systolic, diastolic, and mean, as well as the changes in these parameters between the different time

TABLE 1. Plasma AVP, aldosterone, and ANP levels after surgery

Sample timing	RAP (mm Hg) CABG (n = 11)	RAP (mm Hg) maze (n = 13)	AVP CABG (pg/mL) (n = 11)	AVP maze (pg/mL) (n = 13)	Aldosterone CABG (pg/mL) (n = 11)	Aldosterone maze (pg/mL) (n = 13)	ANP CABG (pg/mL) (n = 9)	ANP maze (pg/mL) (n = 10)
Preoperative	6.3 ± 3.4	5.7 ± 0.6	0.7 ± 0.15	1 ± 0.2	37 ± 16	57 ± 23	25.6 ± 19.7	27.3 ± 30.1
6 h	8.4 ± 2.4	9.1 ± 2.1	9.8 ± 5.5	20.4 ± 6.5	119 ± 49	318 ± 92	18.3 ± 16.1	17 ± 17.4
24 h	9.8 ± 3.1	10.3 ± 2.6	2.1 ± 0.65	4.3 ± 1.3	75 ± 30.5	119 ± 52.5	15.2 ± 14.3	17.4 ± 12.7
48 h	8.5 ± 1.2	8.1 ± 1.9	1 ± 0.3	3.3 ± 1.45	61 ± 26	175 ± 73.5	22.1 ± 11.6	29.4 ± 23.05
72 h	—	—	1.1 ± 0.3	1.5 ± 0.65	112 ± 55	288 ± 183	21.7 ± 24.2	30.2 ± 26.4

AVP, Arginine vasopressin; ANP, atrial natriuretic peptide; CABG, coronary artery bypass grafting; RAP, right atrial pressure. Data are presented as means ± SEM.

points), cardiac index, central venous pressure, blood osmolality, potassium level, cardiopulmonary bypass time, crossclamp time, and plasma ANP levels.

Fluid Retention

Fluid retention was defined and classified as mild, moderate, or severe according to different parameters, including weight, degree of pulmonary congestion, pleural effusion, and peripheral edema. Mild fluid retention included signs of mild pulmonary congestion on physical examination or chest x-ray film, small pleural effusion, the need for O₂ supplement by face mask, 5% weight gain on postoperative day 5, and mild peripheral edema. Moderate fluid retention included clear signs of pulmonary congestion on physical examination or chest x-ray film, moderate size of pleural effusion requiring evacuation, the need for O₂ supplement more than 12 hours per day, weight gain of 5% to 10% on postoperative day 5, and moderate degree of peripheral edema. Severe fluid retention, although rare, included pulmonary edema requiring reintubation, large pleural effusion requiring evacuation, weight gain of more than 10% on postoperative day 5, and severe degree of peripheral edema.

Statistical Analysis

Blood samples taken over time were analyzed by 2-way analysis of variance corrected for repeated measures. Individual means were compared using Student-Newman-Keuls multiple comparison tests. A 2-tailed Spearman's rho coefficient was calculated to assess the correlation between AVP and aldosterone levels to the different parameters mentioned in the previous section. Subgroups analysis was performed using an unpaired *t* test. The null hypothesis was rejected with a *P* value less than .05. Data are expressed as mean ± SEM.

Results

The demographics and other parameters (described in *Methods*) were compared, and no significant differences were found between the 2 groups. Analysis of serial changes in systemic AVP and aldosterone levels after the maze procedure and CABG revealed significant increases in serum hormone levels in both groups postoperatively (Table 1). The blood level of both hormones increased significantly in the postoperative period, peaking within 6 to 24 hours, and then returned to baseline within 3 days after surgery. The

increased levels of AVP and aldosterone were found to be significantly higher in patients after the maze procedure compared with patients after CABG (Figures 1 and 2).

Statistical analysis of the plasma AVP levels (Table 1) of the 2 groups before and after surgery revealed significant effects of both time (*P* < .001) and the maze procedure (*P* = .002). Post hoc analysis using the Student-Newman-Keuls multiple comparison test revealed a significant difference between the means for the first blood sample postoperatively (*P* < .001). Analysis of the aldosterone levels also revealed a significant effect of time (*P* < .001) and the maze procedure (*P* < .05). Post hoc analysis using the Student-Newman-Keuls multiple comparison test revealed significant differences between the means for the first blood sample postoperatively and for the first, second, and fifth samples postoperatively (*P* < .001, *P* = .035, *P* = .01, respectively).

In an attempt to identify possible predictors for the observed differences in AVP and aldosterone levels at specific time points, we used backward stepwise regression analysis for the different parameters that were checked (see *Methods*). For plasma AVP levels, the only significant predictor for the observed difference in the samples taken 6 hours postoperatively was the maze procedure (*P* = .046). Parameters that were significant predictors for the elevated aldosterone levels 6 and 24 hours postoperatively were the maze procedure (*P* = .046 and *P* = .039, respectively) and cardiopulmonary bypass time (*P* = .041 and *P* = .043, respectively). However, in this study we did not find that cardiopulmonary bypass time was significantly longer in the maze procedure group when compared with the CABG group (163.1 ± 37.1 minutes and 133 ± 58 minutes [mean ± SD], respectively, *P* = .155). Aldosterone levels were significantly higher in patients after the maze procedure at 48 hours after surgery as well; however, this is likely related to the fact that all patients in the maze procedure group were treated with spironolactone (75 mg/day) starting 12 hours after the procedure. Spironolactone binds to the mineralocorticoid receptor in the kidney, which is intracellular. The spironolactone cross-reacts with the aldosterone assay in

Figure 1. Perioperative arginine-vasopressin level. *AVP*, Arginine-vasopressin; *CABG*, coronary artery bypass grafting surgery.

Figure 2. Perioperative aldosterone level. *CABG*, Coronary artery bypass grafting surgery.

use for this study. The cross-reactivity of spironolactone in this assay is 0.06%. It is clear that the late increase in aldosterone level is directly related to its pharmacologic effect. However, the higher early levels of the hormone are not related to spironolactone use. We were obligated to use spironolactone in patients after the maze procedure because it has been proven that patients who were not treated with the drug after the procedure were exposed to a relatively higher incidence of fluid retention.

We also performed a subgroup analysis (Table 2) comparing a subgroup of 4 patients who demonstrated a mild degree of fluid retention after the maze procedure (subgroup II) with the rest of the patients after the maze procedure who did not have clinically apparent fluid retention (subgroup I). Interestingly, the AVP levels for the patients in subgroup II were significantly higher when compared with the patients in subgroup I after the maze procedure at 24, 48, and 72 hours postoperatively. The same result was demonstrated for aldosterone in the samples that were drawn 72 hours postoperatively, when all patients were treated with spironolactone.

In this study, no significant difference was found in ANP levels between the 2 groups (Table 1). Furthermore, subgroup analysis for patients with fluid retention revealed no lower level of plasma ANP in the postoperative period.

Discussion

The maze procedure is the most effective surgical approach for the treatment of atrial fibrillation, resulting in a high success rate in abolishing this arrhythmia.¹⁻⁵ In general, patients require relatively high amounts of diuretics to maintain urine output after the maze procedure. This phenomenon is clearly not related to postoperative renal insufficiency or low cardiac output and can lead to clinically significant fluid retention in as many as 12% to 36% of patients.^{4,5}

In animal models, right atrial or bilateral atrial appendectomy reduces the release of ANP and blunts the renal excretion of sodium and water after a large acute volume load.¹³⁻¹⁸ Because the classic maze procedure involves multiple dissections in the left and right atrial tissue, as well as amputation of both right and left atrial appendages, previous clinical studies attributed the fluid retention phenomenon to the abrupt decrease in ANP levels documented after the maze procedure.^{6,7} Amano and colleagues¹⁹ demonstrated that in patients who underwent heart surgery, regardless of whether right atrial appendectomy was performed, plasma levels of ANP failed to increase in response to sodium loading, whereas ANP levels increased preoperatively in both groups after sodium loading. The same study showed that plasma AVP levels were significantly increased by sodium loading both before and after operation in both groups.

The maze procedure involves a large amount of dissection, including incisions and cryosurgery to the right and left atria. As a result, transient right and left atrial dysfunction have been documented.^{20,21} Cardiopulmonary receptors located mainly at the caval-atrial junction, not arterial baroreceptors, are primarily responsible for activation of region associated with regulation of arginine-vasopressin secretion.^{22,23} The lesions induced by the procedure can lead to transient loss of autonomic innervation and in some cases may cause ablation of stretch receptors (cardiopulmonary receptors) in the atria, resulting in a loss of tonic inhibition of AVP release.²⁰

Although the abrupt reduction in ANP levels after the maze procedure may be sufficient to explain some degree of fluid retention, we believed that because of the nature of the operation involving such an extensive dissection within and around the atria tissue, one would expect changes in AVP and aldosterone levels that may lead to additional stimuli for fluid retention and may reflect on a strong stimulus to retain fluids. Indeed, our study demonstrated higher levels of both AVP and aldosterone in patients after the maze procedure

TABLE 2. Plasma AVP and aldosterone levels in patients with and without clinical fluid retention after the maze procedure

Sample timing	AVP (pg/mL) Subgroup I (n = 9)	AVP (pg/mL) Subgroup II (n = 4)	P value	Aldosterone (pg/mL) Subgroup I (n = 9)	Aldosterone (pg/mL) Subgroup II (n = 4)	P value
Preoperative	1.1 ± 0.2	0.9 ± 0.14	.42	82.1 ± 50.5	73.1 ± 26	.88
6 h	8.2 ± 6.7	27 ± 2.6	.19	249.7 ± 81.7	393.1 ± 87.9	.23
24 h	2.9 ± 0.76	6.1 ± 1.25	.03	89.9 ± 23.1	189.7 ± 68.3	.1
48 h	1.4 ± 0.3	6.6 ± 1.3	<.001	183.6 ± 62.1	190.5 ± 57.5	.49
72 h	1.2 ± 0.3	2.5 ± 0.6	.05	172 ± 56.1	554 ± 216.6	.05

Subgroup I: Patients after the maze procedure with no clinically apparent fluid retention. Subgroup II: Patients after the maze procedure with clinical fluid retention. Data are presented as means ± SEM.

when compared with a matched group of patients who underwent CABG. Significantly higher levels of these hormones were found predominantly earlier in the postoperative course, correlating with the clinical occurrence of the postoperative fluid retention in patients after the maze procedure. We find the subgroup analysis very important, although it was limited by the small number of patients with clinically apparent fluid retention, because the hormone levels were higher at various stages of the postoperative course in the patients who demonstrated clinical fluid retention. The current study provides new insights that allow a better understanding of the unique phenomenon of fluid retention after the maze procedure. It will be of interest to evaluate the effect of the new cryosurgical maze procedure on the hormonal secretion profile. This new approach preserves the basic principles of the maze III atrial incisions; however, it is performed using linear cryoprobes as the means to create linear lesions. This approach seems to be less traumatic to the atrial tissue, as can be judged by the much better biatrial contraction early in the postoperative course. Whether this will result in lesser effects on AVP and aldosterone secretion with subsequent reduced degrees of fluid retention and related complications remains to be seen.

In summary, this study documents that the maze procedure results in increased plasma AVP and aldosterone levels and indicates that they, rather than ANP alone, also participate in the tendency for excessive postoperative fluid retention that follows the maze procedure. We believe that these hormone elevations are most likely secondary to a temporary lack of response of the atrial baroreceptors and reflect the presence of a strong stimulus to retain fluids after the maze procedure. Studies are now required to dissect the molecular events and changes in gene expression that lead to the increased susceptibility for fluid retention. These may also enhance the identification of perioperative treatments that will reduce the risk for fluid retention and patients at risk for it.

Limitations of the Study

The data obtained for this study are based on a small group of patients. A major design problem of this study is that at

12 hours after the surgical procedure, spironolactone was given only to the patients after the maze procedure. We are aware that such a drug may have an impact on the results regarding aldosterone levels recorded after 48 hours; however, because spironolactone is an important drug in reducing the fluid retention phenomenon, we were obligated to treat patients after the maze procedure with the drug.

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