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Role of the Atrial Natriuretic Factor in Obstetric Spinal Hypotension

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Background: **In recent years, the concept of prophylactic volume expansion to prevent hypotension caused by spinal anesthesia has been challenged. Investigators have reevaluated the concept of prehydration in the obstetric patient and the physiologic mechanisms involved. This article addresses whether the hypotensive effects attributed to the atrial natriuretic factor are the reason for the apparent failure of prehydration.**

Methods: **Atrial natriuretic factor was measured before (baseline) and 10 min after spinal anesthetic drug injection (control) in 48 healthy pregnant patients scheduled for elective cesarean section. Sixteen patients received hydration with 15 ml/kg crystalloid immediately before spinal anesthesia, 16 patients received the same volume starting with the spinal anesthetic injection, and the remaining 16 patients received no prehydration (control). Blood pressure, heart rate, ephedrine requirements, infused fluids, and urine output were measured.**

Results: **Atrial natriuretic factor concentrations increased significantly in prehydrated patients but not in the control group. There was a significant correlation in the change in atrial natriuretic factor concentrations and urine output but no correlation in the control atrial natriuretic factor concentrations and blood pressure or ephedrine requirements. Ephedrine requirements and blood pressure did not differ significantly among study groups.**

Conclusions: **Atrial natriuretic factor is a potent endogenous diuretic in the pregnant patient but does not appear to be involved in short-term cardiovascular homeostasis after spinal anesthesia. Prehydration appears to prevent hypotension after spinal anesthesia in the obstetric patient.**

SPINAL anesthesia is the most common choice for the anesthetic management of uncomplicated cesarean section in the United States.[1] The most frequent complication with this technique is arterial hypotension.[2] Methods developed for the prevention of hypotension are pelvic tilt and prehydration, a concept that was introduced into clinical practice by Gertie Marx.[3,4] In recent years, however, this concept has been challenged by several investigators.[5,6]

It has been proposed that the atrial natriuretic factor (ANF) may be responsible for the apparent failure of prehydration to prevent spinal anesthesia–related hypotension.[7] ANF has been studied extensively. Its predominant effect is to increase natriuresis.[8] In addition, several other potentially important biologic actions of ANF have been demonstrated *in vitro* and in intact animals, including relaxation of vascular smooth muscle,[9] complex renal effects,[10] and blood pressure reduction.[11] Secreted by the heart, more specifically by atrial cardiomyocytes during normal conditions, but also by ventricular myocytes during cardiac hypertrophy, ANF is now considered an important hormone in the control of blood pressure and salt and water excretion. It now appears that atrial stretch through mechanosensitive ion channels, adrenergic stimulation *via* α_{1A}-adrenergic receptors, and endothelin *via* its endothelin subtype A receptor are major triggering agents of ANF release.

The primary hypothesis tested is whether ANF changes correlate with hypotension. Secondary goals were to address the following questions: do ANF concentrations increase after fluid loading and can hypotension be avoided if the fluid bolus is administered concomitantly with the evolving block (*i.e.*, starting at the time of spinal anesthesia injection)? Because ANF does not increase after only a small fluid bolus,[7] high peak concentrations of the potentially vasodilatory ANF during a period in which the patient is most susceptible to hypotension after spinal anesthesia could presumably be circumvented using the aforementioned "late prehydration."

Materials and Methods

The study protocol was approved by the appropriate institutional review board (University of Florida College of Medicine, Gainesville, Florida). After informed consent was obtained, 48 healthy pregnant women were studied during elective cesarean delivery at term. Indications were a history of cesarean section or malpresentations. Two patients were scheduled for cesarean delivery for fetal reasons (meningomyelocele and diaphragmatic hernia). Exclusion criteria were fetal distress, a maternal medical history significant for any disease state that could affect cardiovascular regulation, obesity (body mass index > 30 kg/m^2), and contraindications to spinal anesthesia. None of the women enrolled in the study were in active labor.

Patients were randomly allocated to receive 15 ml/kg Ringer's lactate over 20 min before the subarachnoid injection (traditional prehydration [TP]), immediately after the subarachnoid injection (late prehydration [LP]), or to receive no prophylactic volume expansion (control group). An 18-gauge peripheral venous cannula was

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Table 1. Maternal Data

	Traditional Prehydration (n = 16)	Late Prehydration (n = 16)	No Prehydration (n = 16)	*P*
Age (yr)	256 ± 6	28 ± 7	27 ± 6	0.655
Weight (kg)	89 ± 19	91 ± 23	85 ± 20	0.740
Height (cm)	163 ± 13	160 ± 10	160 ± 8	0.806
Parity [median (range)]	2 (0–4)	2 (0–3)	1 (0–3)	0.192*
Gravidity [median (range)]	3 (1–8)	3 (1–5)	2 (1–6)	0.069
Total fluids (ml)	2,100 ± 423	2,034 ± 653	1,450 ± 480	0.002†
Baseline recordings				
Systolic pressure (mmHg)	111 ± 9	110 ± 10	107 ± 12	0.544
Mean pressure (mmHg)	82 ± 15	82 ± 8	75 ± 13	0.228
Diastolic pressure (mmHg)	66 ± 12	63 ± 7	59 ± 12	0.169
Heart rate (beats/min)	84 ± 12	87 ± 10	81 ± 12	0.345

Values are expressed as mean ± SD unless otherwise indicated. One-way analysis of variance unless otherwise specified.

* Kruskal-Wallis ANOVA on ranks (normality test failed). † Significant difference.

Total fluids = preload and intraoperative fluid.

placed in the preoperative holding area. Fluids were kept at maintenance infusion rates (100 ml/h) by means of an infusion pump until the prophylactic fluid bolus was started. After completion of the fluid bolus (TP and LP groups), fluids were given as needed (*i.e.*, regulated by the drip rate of the fluid administration set). For ethical reasons, fluids were not restricted in the control group. Intravenous fluids were only infused under pressure for the purpose of prehydration. The amount of infused fluids (total fluids, including prehydration) was recorded at the end of the case. Patients were allowed to use the rest room as needed until they were taken to the operating room. At that time, a urinary catheter was placed. Total urine output was recorded 3 h after the spinal anesthetic injection.

With standard monitors in place, spinal anesthesia was performed with patients in the right lateral supine position using 12 mg hyperbaric bupivacaine (0.75%) combined with 10 μg fentanyl and 0.3 mg preservative-free morphine and a 25-gauge Whitacre needle. Patients were then quickly repositioned onto their back with left lateral pelvic tilt (10–15° leftward rotation of the operating table and a 1,000-ml intravenous bag positioned under the patient's right hip). Blood pressure measurements were obtained every 2 min for 30 min after injection of the spinal anesthetic drug. Thereafter, blood pressure readings were obtained at 5-min intervals.

Two blood samples for the measurement of the ANF were obtained: the first at the time of intravenous tube placement (baseline), the second at 10 min after subarachnoid injection (control). Blood samples were then spun and stored on dry ice until analyzed. Plasma ANF samples were extracted using a Sep-Pak C-18 column (Waters, Milford, MA), and were then assayed by radioimmunoassay extraction using rabbit antihuman ANF antiserum. The bound–free separation was achieved using goat antirabbit γ globulin (second preparation). The assay sensitivity is 10 pg/ml. Human reference values are 25–77 pg/ml. Details of this method have been published previously.[12]

Baseline blood pressure and heart rate were the calculated means of five independent readings obtained in the preoperative holding area with the patient in the supine position with pelvic tilt, similar to the surgical position. After the spinal anesthetic injection, hypotension was treated according to the observed degree of reduction in mean arterial blood pressure (MAP). Hypotension was defined as a decrease in MAP greater than 20% from baseline values. Ephedrine (5 mg) was administered intravenously if MAP decreased more than 20% but less than 30%, and 10 mg ephedrine was given if the blood pressure decreased more than 30%. Ephedrine administration was repeated according to subsequent blood pressure readings (*i.e.*, every 2 min as needed).

Table 2. Neonatal Data

	Traditional Prehydration (n = 16)	Late Prehydration (n = 16)	No Prehydration (n = 16)	*P*
1-min Apgar score [median (range)]	9 (7–9)	9 (7–9)	9 (7–9)	0.514
5-min Apgar score [median (range)]	9 (8–9)	9 (8–9)	9 (8–9)	0.418
Bicarbonate (mEq/l)	23.7 ± 1.9	23.3 ± 1.6	24.0 ± 1.4	0.488
Base deficit (mEq/l)	1.0 ± 3.4	0.5 ± 3.1	1.7 ± 2.1	0.105
Umbilical–venous pH	7.29 ± 0.08	7.29 ± 0.06	7.30 ± 0.05	0.901
Umbilical–venous P_{CO_2} (mmHg)	49.5 ± 5.5	50.4 ± 5.7	50.2 ± 6.1	0.932

Values are expressed as mean ± SD and compared using one-way analysis of variance unless specified otherwise.

P_{CO_2} = partial pressure of carbon dioxide.

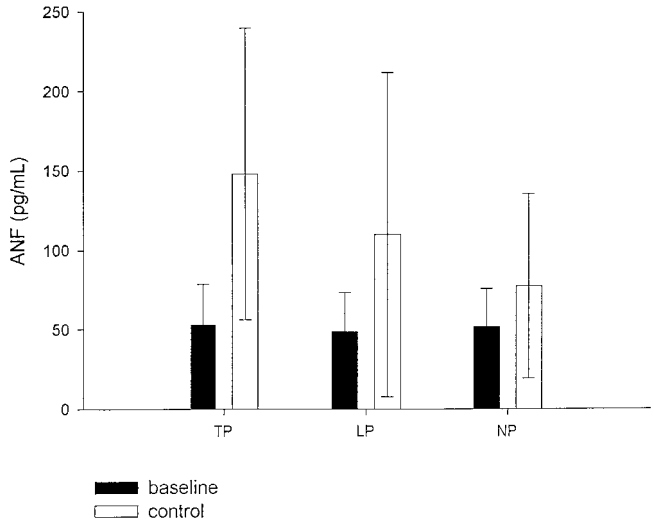

Fig. 1. Baseline and control values of the atrial natriuretic factor (ANF). The height of the solid bars corresponds to group means, and whisker bars indicate SD. TP = traditional prehydration; LP = late prehydration; NP = no prehydration.

Study Design and Data Analysis

A sample size (n = 15) for each of the three study groups was determined to provide 80% power at a significance level of $\alpha = 0.05$. The power analysis was calculated to detect a 50-pg/ml difference in group means assuming a 40-pg/ml SD. In this study, one additional subject was enrolled in each group (n = 16 in all study groups) in case a subject had to be excluded.

With respect to calculated correlations, it should be noted that our sample size of 48 allowed us to detect the absolute value of a correlation coefficient of 0.6 or larger with a power of 99.6% at a significance level of 0.05. There is only a 0.4% risk of a false-negative result if the absolute value of the population correlation coefficient was 0.6.

Data are presented as mean ± SD unless specified otherwise. The three study groups were compared using raw data with a one-way analysis of variance (ANOVA) where applicable. Before executing the ANOVA, data were tested for normality (Kolmogorov-Smirnov test) and equal variance. If any of those tests failed, data were compared using a Kruskal-Wallis one-way ANOVA on ranks. The Tukey test was used for *post hoc* multiple comparisons. The incidence (frequency) of hypotension among study groups was compared using a chi-square test. Correlations were calculated with the Pearson product moment correlation for normally distributed data and with the Spearman rank order correlation for non-normally distributed data. Baseline and control ANF values were compared using the Student *t* test within each group, whereas ANF values between groups were compared using a one-way ANOVA.

For the purpose of statistical analysis, the 30-min observation period was divided into two segments: the first 10 min after spinal anesthetic injection and the latter 20 min. The rationale for this measure is provided in the Discussion. Ephedrine requirements were compared at the 2-, 4-, 6-, 8-, and 10-min time periods, and the average ephedrine requirements from time 0 to 10 min and from time 12 to 30 min after spinal anesthetic injection were compared (one-way ANOVA). The relative change in MAP was compared with a repeated one-way ANOVA for two time periods (0–10 and 12–30 min). The significance level was adjusted to reflect multiple comparisons.

Results

Patient groups were similar with respect to age, height, weight, parity, baseline heart rate, and blood pressure (table 1). The spinal anesthetic used resulted in a similar sensory block (block height at 5 min). Patients who were randomized to prehydration (TP and LP groups) received more total fluids than patients who did not receive prehydration.

The neonates born to mothers in the three study groups did equally well. There was neither a significant difference in 1- or 5-min Apgar scores, nor in umbilical venous blood gas values (table 2).

Baseline values of ANF (table 3 and fig. 1) were similar among study groups. The ANF increase (baseline *vs.*

Table 3. Atrial Natriuretic Factor and Hypotension: Comparison of Study Groups

	Traditional Prehydration (n = 16)	Late Prehydration (n = 16)	No Prehydration (n = 16)	*P*
ANF, UOP				
Baseline ANF (pg/ml)	53 ± 26	49 ± 25	52 ± 24	0.874
Control ANF (pg/ml)	147 ± 92	110 ± 102	77 ± 58	0.034*
3-h urine output (ml)	333 ± 254	245 ± 244	177 ± 185	0.101
Hypotension				
Incidence of hypotension†	81%	75%	69%	0.717
Average MAP decrease (%)†	−13 ± 17	−7 ± 13	−6 ± 13	0.318
Intravenous fluids (ml)‡	2,100 ± 423	2,034 ± 653	1,250 ± 480	0.002*§

Data are presented as mean ± SD when applicable.

* One-way analysis of variance on ranks and Tukey multiple comparison *post hoc* test. † Observations limited to the first 10 min after subarachnoid injection. ‡ Includes prehydration. § Statistically significant difference.

ANF = atrial natriuretic factor; UOP = urine output; MAP = mean arterial pressure.

Table 4. Ephedrine Requirements for the Time Points 2, 4, 6, 8, and 10 Min and for the Time Intervals 2–10 Min and 12–30 Min

Time (min)	Traditional Prehydration (n = 16)	Late Prehydration (n = 16)	No Prehydration (n = 16)	*P*
2	3.4 ± 4.4	1.9 ± 4.0	1.3 ± 3.4	0.283
4	5.0 ± 4.1	2.2 ± 3.6	1.9 ± 3.6	0.045*
6	4.7 ± 4.3	2.2 ± 3.2	3.8 ± 4.6	0.226
8	2.2 ± 4.1	1.6 ± 3.5	1.9 ± 3.6	0.893
10	0.9 ± 2.7	0.6 ± 2.5	0.6 ± 1.7	0.912
2–10	3.3 ± 4.1	1.7 ± 3.4	1.9 ± 3.6	0.437
12–30	1.0 ± 2.3	0.6 ± 2.1	0.4 ± 1.5	0.666

Data are mean ± SD.

* Significant difference (analysis of variance), but not significant after *post hoc* comparison (Tukey).

control values) was significant within the TP and LP groups but not in the group that did not receive prehydration.

The incidence of hypotension (table 3) was not statistically different: 81% in the TP group, 75% in the LP group, and 69% in the no-prehydration group. MAP and ephedrine requirements (table 4, figs. 2 and 3) did not differ among study groups for both observation periods (0–10 min and 12–30 min).

Correlations were calculated for several data pairs (table 5 and figs. 4–6): ANF change–ephedrine requirements (during the first 10 min), ANF change–MAP change (comparing baseline MAP with average MAP during the first 10 min), as well as ANF–3-h urine output and ANF–total fluids. A significant correlation could be established between the ANF (control values) and the 3-h urine output and between ANF (control) and total fluids. There was neither a significant correlation between ANF and ephedrine requirements nor between ANF and MAP decline (comparing all groups as well as individual study group).

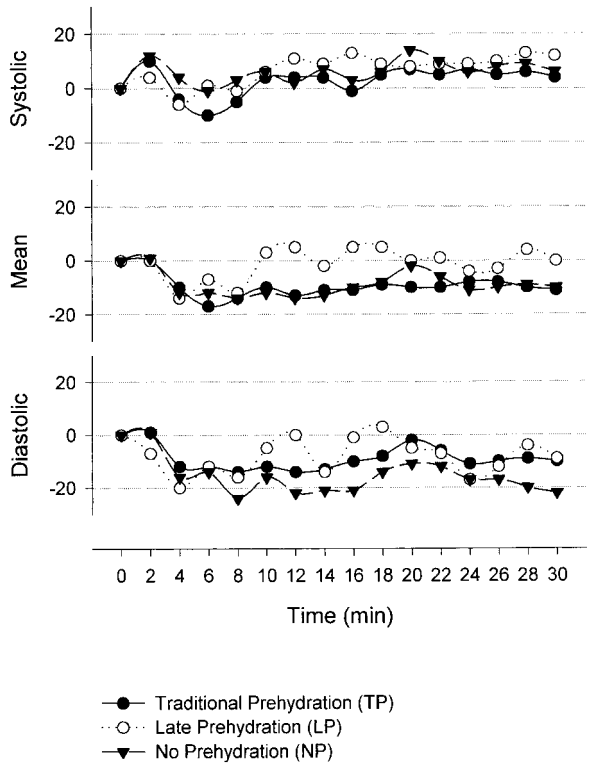

Fig. 2. Average blood pressure readings over time. Blood pressure measurements did not differ significantly (repeated measures of one-way analysis of variance).

Discussion

Research on cardiovascular physiology received much attention when, in 1981, De Bold *et al.*[13] demonstrated that a crude extract of atrial tissue from rat hearts, when injected into anesthetized bioassay rats, caused a large and rapid increase in urinary excretion of sodium chloride. Subsequently, several structurally related peptides, collectively known as ANF, have been isolated from rat and human atria, sequenced and synthesized, and shown to mimic the natriuretic and hypotensive effects of atrial extracts.[14] Among many other medical conditions, pregnancy, with its associated cardiovascular changes, ap-

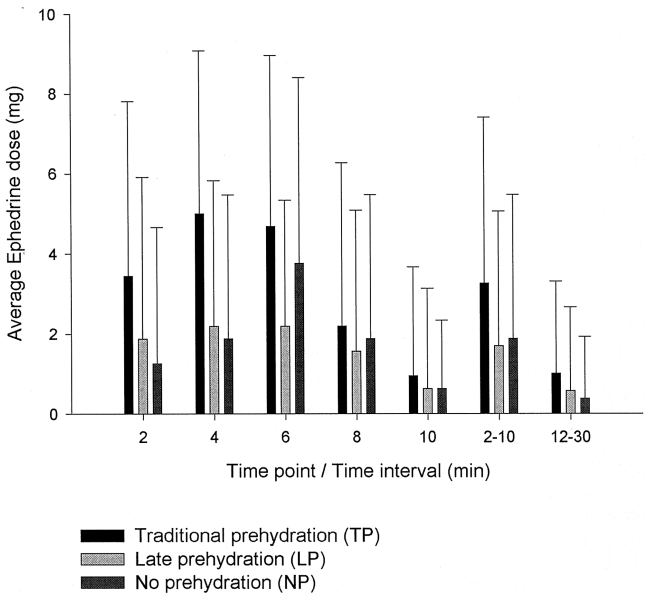

Fig. 3. Average ephedrine requirements are presented at time points 2, 4, 6, 8, and 10 min. The average requirements over the time periods 2–10 min and 12–30 min are also displayed. The height of the solid bars corresponds to group means, and whisker bars indicate SD.

Table 5. Correlations

Correlation	Correlation Coefficient	*P* Value	95% Confidence Interval
ANF–urine output	0.559	< 0.001*	+0.32, +0.73
ANF–ephedrine requirements	0.010	0.949	−0.3, +0.3
ANF–MAP	−0.090	0.550	−0.38, +0.21

* Significant correlation.

ANF = atrial natriuretic factor; MAP = mean arterial pressure.

pealed to researchers interested in ANF.[15,16] In 1991, Datta *et al.*[17] reported increased ANF concentrations in pregnant patients scheduled for elective cesarean section with spinal anesthesia when compared with nonpregnant controls. In another study, Pouta *et al.*[7] confirmed the ANF increase after volume expansion in pregnant patients and suggested vasodilatory properties of ANF as the reason for the apparent failure of prehydration to prevent post–spinal anesthesia hypotension. Unfortunately, Pouta *et al.* did not have a control group in their study, and investigators did not report the time course of blood pressure or correlate ANF blood sampling with hypotension. Therefore, statements regarding the physiologic role of ANF were highly speculative. In this study, ANF concentrations were obtained in preloaded patients scheduled for elective cesarean section, compared with nonpreloaded controls, and scheduled at a time when spinal hypotension was expected.

In our study, ANF control concentrations were obtained 10 min after subarachnoid injection of local anesthetic because hypotension after spinal anesthesia can be observed within the first 10 min in the vast majority (> 90%) of patients.[18] ANF concentrations increased significantly in the TP and LP groups. The lesser increase of ANF in the LP group is consistent with previous research demonstrating a delay (approximately 30 min) in the secretion of ANF after the administration of a fluid bolus.[19,20] Because pregnancy is associated with an expansion of the extracellular fluid, it has been called into question whether a fluid bolus during pregnancy would trigger an ANF increase at all. Hatjis *et al.*[21] found no ANF increase after a fluid bolus in pregnant patients when compared with nonpregnant controls. In contrast, several other groups demonstrated what was confirmed in our study: that ANF increased after an intravenous fluid bolus in term pregnancy.

There was no significant increase in the group of patients who did not receive prehydration. If ANF, in fact, played a major role in preventing prehydration from being effective, one would have expected an inverse correlation of ANF increase and blood pressure change. The lack of such a

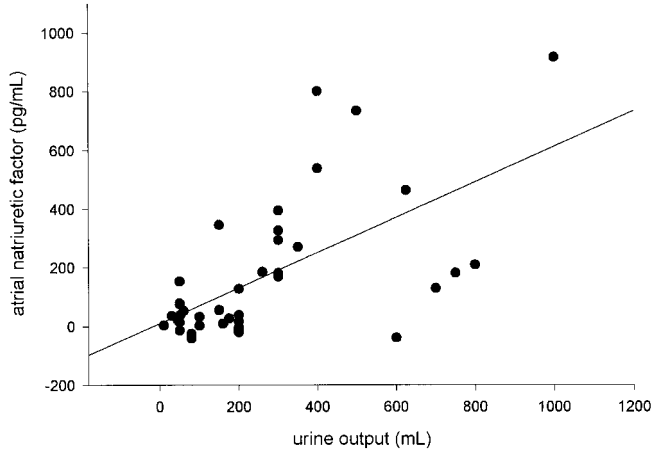

Fig. 4. Atrial natriuretic factor *versus* urine output. There is a significant correlation, with $P < 0.001$ and a correlation coefficient of 0.56.

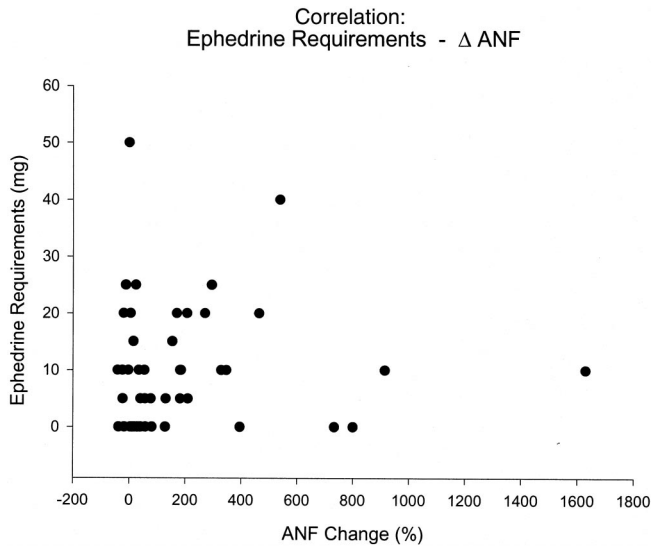

Fig. 5. Ephedrine requirements *versus* atrial natriuretic factor (ANF) change. There are no significant relations between ephedrine requirements and the observed change in ANF. The correlation coefficient is 0.00966, and $P = 0.949$.

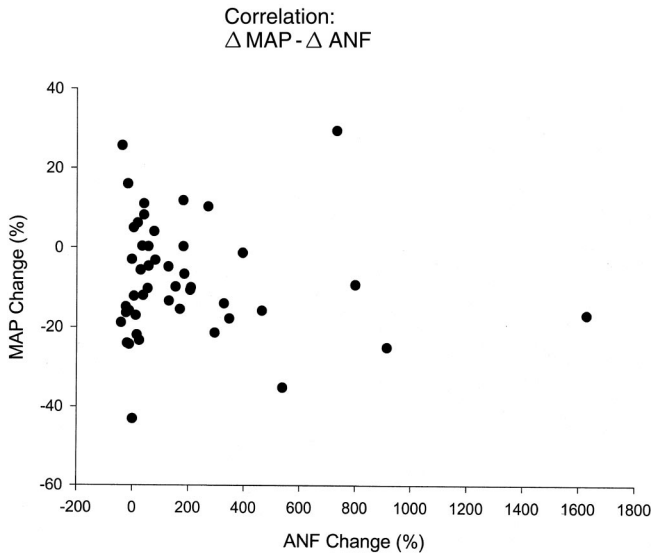

Fig. 6. There are no significant relations between blood pressure changes and the observed change in atrial natriuretic factor (ANF). The correlation coefficient is −0.0903, and $P = 0.550$. MAP = mean arterial pressure.

correlation calls into question the concept of ANF being an important contributor to post–spinal anesthesia hypotension. It appears that a certain percentage of patients remain hemodynamically stable regardless of their ANF concentration, and other patients develop hypotension despite low ANF concentrations. This finding does not completely negate the concept that ANF may play a role in the failure of prehydration to prevent hypotension. After all, prehydrated patients show higher ANF concentrations and, with respect to hypotension, did not fare better than the group without prehydration. However, differences in ANF concentrations as the sole factor certainly cannot account for the fact that some patients develop hypotension whether they have been preloaded or not.

A supporting argument for the theory that ANF acts as a vasodilator and participates in acute volume homeostasis is based on research demonstrating the vasodilatory properties of ANF.[22] However, we learned from a pharmacokinetic model that ANF infusions that produced vasodilation in the aforementioned study[22] were supraphysiologic and resulted in plasma concentrations of ANF as high as 1,185 ± 321 pg/ml.[23] We did not observe an inverse correlation of either ephedrine requirements or blood pressure decline to ANF controls in our study. The lack of such a correlation is inconsistent with a physiologic effect of ANF on acute blood pressure regulation.

We discovered a significant correlation between ANF and 3-h urine output ($P < 0.001$). This important finding is in line with animal and human data on the renal effects of ANF.[8] Thus, ANF may play an important role as a regulator of urine output in patients who receive an intravenous fluid bolus.

It has been suggested that adrenergic agonists can potentially liberate ANF.[24] However, the lack of a correlation between ephedrine doses and ANF control values in our study argues against a direct ANF-liberating effect of adrenergic agonists, a potentially confounding factor. Finally, it was found that all study groups, regardless of the amount and timing of prehydration, did not show a significant difference with respect to ephedrine requirements, incidence of hypotension, or average blood pressure change. This observation, once again, challenges the effectiveness of prehydration. It should be recognized that the sample size determination (power) of the current study was based on the expected distribution of ANF values, not blood pressure. Therefore, the lack of a significant difference should be interpreted with caution.

In summary, the current study demonstrates that ANF functions as an endogenous diuretic in response to an acute volume challenge. A physiologic role of the ANF in acute blood pressure regulation appears unlikely. We confirm that crystalloid prehydration does not prevent hypotension after spinal anesthesia. Physiologic adaptation mechanisms such as a reduction in systemic vascular resistance and an increased fluid shift into the interstitium after the Starling forces may prevent traditional crystalloid prehydration from being effective.

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