Physiology

LEVELS OF PLASMA ATRIAL NATRIURETIC PEPTIDE IN NORMAL AND PREECLAMPTIC PREGNANCIES

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SUMMARY: Our aims were to clarify the possible role of atrial natriuretic peptide (ANP) in the pathophysiology of preeclampsia, to study the relationship between ANP levels and gestational age, and to evaluate the correlation between ANP and blood pressure findings in preeclamptic pregnancies. Plasma ANP levels were measured by RIA in normotensive (n=10) and preeclamptic (n=13) pregnant women in their third trimesters. The mean (± SE) plasma ANP levels in the normal and preeclamptic pregnant women were 33.33 ± 8.75 and 44.62 ± 7.02 pg/ml, respectively, the higher level in the hypertensive group being statistically non-significant. Despite plasma volume reduction in preeclampsia, elevated plasma ANP levels suggest that ANP may be released in response to a rise in intra-atrial pressures secondary to hypertension in this state. It is also concluded that ANP, which is also a potent vasorelaxant, can induce compensatory mechanisms following the increased responsiveness of the vascular bed to angiotensin II in the preeclamptic state. What is more, higher ANP levels may also explain volume reduction characteristic of preeclampsia. Plasma ANP levels correlation with the gestational age non-significantly and negatively in the preeclamptics (r=-0.16). A non-significant, positive correlation existed between plasma ANP levels and mean blood pressure in the preeclamptic patients (r=0.38).

Key Words: Atrial natriuretic peptide, pregnancy, preeclampsia.

INTRODUCTION

In normal pregnancy there is approximately 50 percent increase in the total extra-cellular fluid and blood volumes, which are the result of approximately 900 mmol sodium retention (2, 22). The degree of plasma volume expansion in normal pregnancy is significantly and positively correlated with fetal birth weight (2). There also exists profound peripheral arterial vasodilation in normal pregnancy, which leads to a condition "sensed" as an under fill state, despite volume expansion to this degree (22). In preeclampsia, much research documents relative hypovolemia in comparison with normal pregnancy (2, 9, 12, 23), and these data suggest that preeclamptic pregnants "sense" this reduced plasma volume, since sodium retention in the face of intravascular volume contraction is an expected homeostatic renal response (2). In other words, reduced plasma volume is not appropriate for the vasoconstricted state of preeclampsia, and therefore "not sensed" as normal, thus leading to sodium retention in preeclampsia (2).

Atrial natriuretic peptide (ANP), which is a potent natriuretic and vasorelaxant substance existing in granules of the heart's atria, has an important role in volume homeostasis, and the main stimuli to ANP release seem to be volume-dependent in response to increased atrial pressure (5, 15). However, though plasma volume is reduced in preeclampsia, plasma ANP concentrations have been reported as increased, with the highest values in patients with more severe preeclampsia (1,8,9,16,17,19, 24).

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The aims of this study were: 1) to determine the potential role of ANP in the prediction and course of preeclampsia, 2) to study the effect of gestational age on plasma ANP levels in the preeclamptics and 3) to evaluate the correlation between ANP and blood pressure findings in preeclamptic patients.

MATERIALS AND METHODS

Ten normal pregnant women in their third trimesters were studied; they were selected from those admitted to Obstetrics and Gynecology Outpatient Clinics of Çukurova University Hospital for their periodic pregnancy examinations. Thirteen preeclamptic patients in their third trimesters were studied; they were selected from those admitted to the same hospital. All women ranged in age from 18 to 43 years, and no evidence of renal and/or cardiovascular disorders was present. Since hypertension in the third trimester is defined as a blood pressure of 140/85 mmHg or greater that is sustained during repeated measurements for 6 hours (6), all selected preeclamptic women had blood pressures ≥140/85 mmHg, associated with proteinuria and edema. Normal pregnant subjects were between 30 and 39 weeks of gestation; preeclamptic women were between 28 and 39 weeks of gestation. None of the pregnant women had any previous stillbirths. The clinical data of the pregnant groups are shown in Tables 1 and 2.

All of the women had been admitted to Çukurova University Hospital at least 2 days before the study was performed. The normal pregnant women were prescribed a diet consisting of approximately 170 meq/day of sodium, and the subjects with preeclampsia were given about 120 meq/day of sodium. None of the women took any drugs before and/or during the study, other than iron or vitamin supplements.

The same examiner measured the blood pressure every 4 hours along 2 days, with a manual sphygmomanometer at the right brachial artery after the women had been kept in the sitting position for ≥ 15 minutes. On the day of study blood pressures were evaluated by the same examiner as described above, and simultaneously, venous blood samples were collected in pre-chilled tubes (Becton Dickinson Vacutainer Systems, England) kept in crushed ice containing sodium ethylenediaminetetra-acetic acid (EDTA-Na_2). All blood samples were taken in the morning, between 9.00-10.00 a. m. 400 kalikrein inhibitor unit (KIU) Trasylol/ml (Bayer, Leverkusen, West Germany) was added to venous blood samples that would be run for ANP levels. All blood samples were kept in crushed ice, and the plasma was separated without delay by centrifuge for 15 minutes at 4°C, using 1800-2000xg. Hemolyzed samples were not used for ANP evaluation. Plasma samples were stored at -70°C until RIA (radio immunoassay) would be performed. Thawing of the samples before the assay were carried out taking care that the temperature did not exceed 4°C. Repeated freeze-thaw cycles were avoided.

Plasma ANP levels were evaluated by RIA (ANP 1 RIA kit, Incstar Corp., U. S., Cat. No: 22750). The direct measurement of ANP in plasma by RIA has proven to be unreliable due to the multiple nonspecific substances found in plasma and possibly other unknown causes (11). To improve the accuracy of the assays, cartridge extraction methods have been developed for plasma to purify the samples prior to being assayed (14, 20). In our study, ANP was extracted from plasma with an octadecasilyl-silica (ODS-silica) minicolumn (Sep-Pac C18); then the ANP from each minicolumn was eluted by adding 4% acetic acid in 86% ethanol, and the elutes were collected in polystyrene tubes (14,18,20). The eluates were evaporated to complete dryness in a 37°C water bath using compressed nitrogen and ANP levels were evaluated by RIA in dried samples.

Statistical evaluation was performed with Mann-Whitney U test and correlation-regression analysis (CSS Statistical). The values were expressed as the mean ±SEM.

RESULTS

ANP levels of 234 women in their third trimesters of pregnancy were tested. ANP values of the pregnant women are shown in Figure 1. Table 3 shows the mean (±SE) values of plasma atrial natriuretic peptide in the pregnant groups. In the normal and preeclamptic pregnant groups, mean plasma ANP values were 33.33±8.75 and 44.62±7.02 pg/ml, respectively. Although mean plasma ANP value of the preeclamptic pregnants was higher than that of the normal pregnants (Figure 2), this difference was found to be non-significant (p=0.264>0.05).

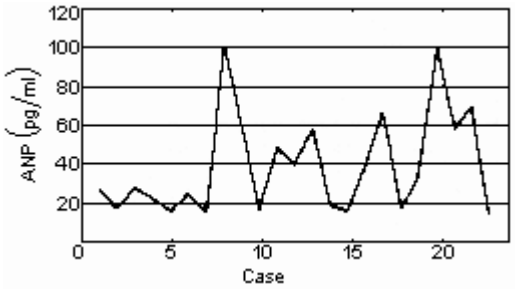

Figure 1: ANP values of the pregnant women. Cases from one to ten are normal pregnants; cases from eleven to twenty-three are preeclamptics.

Table 1: Clinical data on the thirteen women with preeclampsia.

Patient no.	Age (years)	Weight (kg)	Gravidity	Parity	Abortus	Gestational age at the study (weeks)	BP1 (mmHg)	MBP2 (mmHg)
1	38	75	3	2	0	33	180/90	120.000
2	39	68	7	5	1	28	160/90	113.333
3	28	85	3	0	2	39	140/100	113.333
4	31	65	5	2	2	35	170/110	130.000
5	39	110	8	5	2	36	150/100	116.666
6	21	75	1	0	0	37	150/100	116.666
7	33	110	4	3	0	34	160/110	126.666
8	36	69	4	3	0	32	180/120	140.000
9	29	65	2	0	1	28	170/85	113.333
10	33	76	7	3	3	31	160/110	126.666
11	33	80	6	2	3	34	190/130	150.000
12	34	53	5	3	1	32	190/130	150.000
13	43	90	13	11	1	36	150/90	110.000

(1) Blood pressure at time of sampling

(2) Mean blood pressure

Table 2: Clinical data on the normal and preeclamptic pregnants (mean ± SE).

	Age (years)	Weight (kg)	Parity	Gestational age at the study (weeks)	BP1 (mmHg)		MBP2 (mmHg)
					systolic	diastolic	
NP* (n=10)	25.70±1.68	67.50±1.42	0.80±0.29	34.80±0.96	117.00±2.60	73.00±3.00	87.67±2.49
PE* (n=13)	33.62±1.58	78.54±4.67	3.00±0.81	33.46±0.91	165.39±4.47	105.00±4.16	126.67±3.76

(1) Blood pressure at time of sampling

(2) Mean blood pressure

(*) Normal pregnancy

(**) Preeclampsia

Table 3: Plasma ANP values in the pregnant groups.

ANP (pg/ml)	Normal pregnancy (n=10)	Preeclampsia (n=13)
Mean ± SE	33.33±8.75	44.62±7.02
Minimum value	15.47	15.07
Maximum value	101.59	98.73
p=0.264>0.05		

A significant, negative correlation existed between plasma ANP levels and mean blood pressure (MBP) in the healthy pregnants (r=-0.65, p=0.04<0.05; Figure 3), whereas the same correlation was found to be non-significant and positive in the preeclamptic subjects (r=0.38, p=0.2>0.05; Figure 4).

Plasma ANP levels correlated with the gestational age non-significantly and negatively both in normal pregnants and preeclamptic patients (r=0.29, p=0.42 and r=-0.16, p=0.59, respectively).

Plasma ANP levels correlated with the maternal age non-significantly and positively in the normal pregnants (r=0.33, p=0.35), but negatively in the preeclamptic group (r= 0.25, p=0.4).

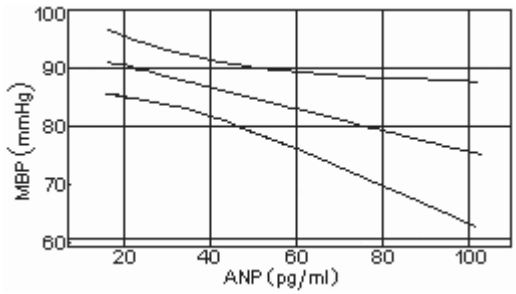

Figure 2: Mean values of ANP in the pregnant groups (NP: Normal pregnancy; PE: Preeclampsia).

DISCUSSION

Mean plasma ANP value in the third trimester preeclamptic subjects was found to be higher than that of the normotensive pregnants (44.62±7.02 and 33.33±8.75 pg/ml, respectively), the difference between two groups being non-significant (Table 3, Figure 2). Plasma ANP values in normal pregnants and preeclamptic subjects were found to range widely distributed (from 15.47 to 101.59 and 15.07 to 98.73 pg/ml, respectively).

It is known that release of ANP is stimulated by atrial distention or stretch and that plasma ANP values increase in response to plasma expansion (5, 10). It has been reported in most studies that the mean plasma ANP value is significantly higher in preeclampsia than in normal pregnancy (1,8,9,16,17,19,24).

In the case of preeclampsia, of which vasoconstriction is a dominant feature, there is early "over-expansion" of the plasma volume followed by "escape" from this positive sodium balance and consequent reduction of the plasma volume (2). Despite reduction of plasma volume in preeclampsia (2, 9), this condition

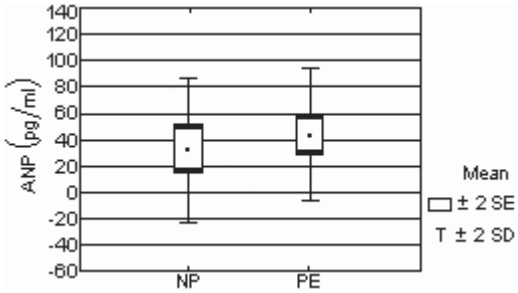

Figure 3: A significant, negative strong correlation exists between ANP levels and mean blood pressure (MBP) in the normal pregnants (n=10, r =-0.65, p=0.04<0.05).

is associated with increased plasma concentrations of plasma ANP, which increase still further with the severity of the disease (25). Therefore, increased plasma ANP levels in preeclampsia can not be explained by the effect of plasma volume. The mechanism of the observed rise in ANP concentrations in preeclampsia may be related to a rise in intra-atrial pressures secondary to hypertension (7), since it was reported that pregnant women with proteinuria or edema but without hypertension had normal plasma ANP levels (13). In a study, it has been determined that an increase in mean pulmonary artery wedge pressure caused an increase in plasma ANP levels, and that mean pulmonary artery wedge pressure correlated with plasma ANP values (21). Carlsson (3) reported that although central venous pressure was within normal ranges in preeclampsia, mean pulmonary artery wedge pressure increased above the normal limit. This findings indicates that increased plasma ANP values in preeclampsia may be due to the distension or stretching of the left atrium.

Elevated ANP levels in preeclampsia may also be due to decreased renal clearance of the peptide, due to

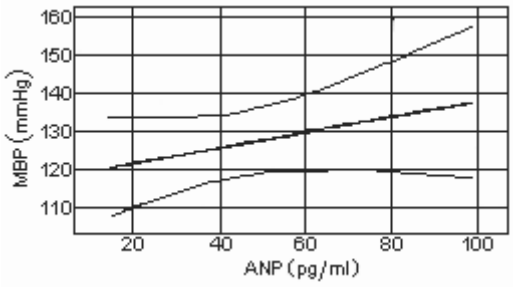

Figure 4: A non-significant, positive correlation exists between ANP levels and mean blood pressure (MBP) in the preeclamptic subjects (n=13, r =0.38, p=0.20>0.05).

a diminished glomerular filtration rate. ANP is cleared not only by kidneys, but also by the liver and skeletal muscle (4). Because our preeclamptic subjects did not exhibit significant renal or hepatic impairment, decreased clearance possibly did not contribute to the elevated ANP levels determined in this study. Another, but less likely explanation for the elevated ANP levels in preeclampsia may be release of ANP from extra-cardiac sites (7).

Increased plasma ANP levels in preeclampsia, which is also supported by our findings, may reflect a mechanism of compensation which operates in response to water and sodium retention in preeclamptic pregnancy. Higher ANP values may also explain volume reduction characteristic of preeclampsia, by causing both a sodium wastage and failure of water- and sodium-saving factors expand maternal volume adequately, since it is a fact that ANP produces marked and sustained suppression of both renal renin secretion and plasma renin levels (15). What is more, it may be concluded that ANP, which is also a potent vasorelaxant, can induce compensatory mechanisms following the increased responsiveness of the vascular bed to angiotensin II in the preeclamptic state (15). Therefore, these data suggest a compensatory role of ANP in the prevention of blood pressure increase, but this explanation has not been proved by our other finding that a non-significant, positive correlation exists between plasma ANP levels and mean blood pressure in the preeclamptic group (r=0.38, p=0.2; Figure 4). Being similar with our finding, Fievet (9) has also reported a positive correlation between plasma ANP and mean arterial pressure in hypertensive pregnant women. In contrast to that in preeclamptics, we found a significant, negative correlation between plasma ANP levels and mean blood pressure in the healthy pregnants. (r=-0.65, p=0.04; Figure 3); these data indicate that ANP tends to decrease arterial pressure in the normal pregnant women, but not in preeclamptics; therefore there may be a failure of blood pressure lowering factors in preeclampsia to dilate maternal vasculature efficiently. Moreover, the positive correlation that we found between plasma ANP levels and MBP in the preeclamptic group may lead to the suggestion that ANP may be released in response to a rise in intra-atrial pressures secondary to hypertension in the state, and this conclusion is supported by some other authors' findings (7,13).

The non-significant, negative correlations that we determined between plasma ANP levels and gestational age in both groups indicate decreased release of ANP in relation to gestational age in normal and preeclamptic pregnancies.

Plasma ANP levels correlating with the maternal age non-significantly and positively in the normal pregnants (r=0.33), but negatively in the preeclamptic group (r=-0.25), may suggest that elder preeclamptics are more prone to water and sodium retention and /or to vasoconstriction than the elder normal pregnants, and the course of preeclampsia becomes worse in advanced ages.

REFERENCES

1. Bond AL, August P, Druzin ML, et al : Atrial natriuretic factor in normal and hypertensive pregnancy. Am J Obstet Gynecol, 160:1112-1116, 1989.

2. Brown MA : Sodium and plasma volume regulation in normal and hypertensive pregnancy: A review of physiology and clinical implications. Clin Exper Hyper in Pregnancy, B7:265-282, 1988.

3. Carlsson C : Cardiovascular changes in preeclampsia. Acta Obstet Gynecol Scand, 118:121-122, 1984.

4. Crozier IG, Nicholls G, Ikram H, et al : Atrial natriuretic peptide in humans: Production and clearance by various tissues. Hypertension, 8:11-16 1986.

5. Cunningham SL : The physiology of body fluids. In: Text book of Physiology, Vol 2, 21st ed, pp 1102-1103, Ed by HD Patton, AF Fuchs, B Hille, et al. WB Saunders Comp, Philadelphia, 1989.

6. Davison JM, Lindheimer ND : Hypertension in pregnancy. In: Maternal and Fetal Medicine. Gynecology and Obstetrics, Vol 3, Ed by R Depp, DA Eschenbach, JJ Sciarra. Harper and Row Publ, Philadelphia, Revised Ed, 1987.

7. Elias AN, Vaziri ND, Padian MR, et al : Atrial natriuretic peptide and arginine vasopressin in pregnancy and pregnancy-induced hypertension. Nephron, 49:140-143, 1988.

8. Fieved P, Fournier A, De Bold A, et al : Pregnancy-induced hypertension and preeclampsia developed in spite of high circulating levels of cardionatrin. Arch Mal Coeur, 80:936-941, 1987.

9. Fievet P, Fournier A, de Bold A, et al : Atrial natriuretic factor in pregnancy-induced hypertension and preeclampsia: Increased plasma concentrations possibly explaining these hypovolemic states with paradoxical hyporeninism. Am J Hypertens, 1:16-21, 1988.

10. Ganong WF : Review of Medical Physiology. 15th ed. Appleton and Lange Publ, USA, 1991.

11. Gutkowska J, Bonan R, Roy D, et al : Atrial Natriuretic factor in human plasma. Biochem Biophys Res Commun, 139:287-290, 1986.

12. Hays PM, Cruikshank DP, Dunn LJ : Plasma volume determination in normal and preeclamptic pregnancies. Am J Obstet Gynecol, 151:958-966, 1985.

13. Hirai N, Yanaihara T, Nakayama T, et al : Plasma levels of atrial natriuretic peptide during normal pregnancy and in pregnancy complicated by hypertension. Am J Obstet Gynecol, 159:27-31, 1988.

14. Lang RE, Tholken H, Ganten D, et al : Atrial natriuretic factor a circulating hormone stimulated by volume loading. Nature, 314:264-267, 1985.

15. Laragh JH, Atlas SA : Atrial natriuretic hormone: A regulator of blood pressure and volume homeostasis. Kidney Int, 34:564-571, 1988.

16. Matzen S, Nielsen J, Christensen J, et al : Atrial natriuretic peptide concentrations in umbilical cord plasma prom preeclamptic women. Clin Physiol, 11:119-126, 1991.

17. Mikkelsen AL, Schutten HJ : Plasma concentration of atrial natriuretic peptide in normal pregnant women and in pregnant women with preeclampsia. Gynecol Obstet Invest, 31:192-195, 1991.

18. Mayamoto S, Shimokawa H, Sumioki H, et al : Circadian rhythm of plasma atrial natriuretic peptide, aldosterone and blood pressure during the third trimester in normal and preeclamptic pregnancies. Am J Obstet Gynecol, 158:393-399, 1988.

19. Miyamoto S, Shimokawa H, Sumioki H, Nakano H : Physiologic role of endogenous human atrial natriuretic peptide in preeclamptic pregnancies. Am J Obstet Gynecol, 160:155-159, 1989.

20. Miyata A, Kangawa K, Toshimori T, et al : Molecular forms of atrial natriuretic polypeptides in mammalian tissues and plasma. Biochem Biophys Res Commun, 129:248-251, 1985.

21. Sato F, Kamoi K, Wakiya Y, et al : Relationship between plasma atrial natriuretic peptide level and atrial pressure in man. J Clin Endocrinol Metab, 63:823-827, 1986.

22. Schrier RW, Briner VA : Peripheral arterial vasodilatation hypothesis of sodium and water retention in pregnancy: Implications for pathogenesis of preeclampsia-eclampsia. Obstet Gynecol, 77:632-639, 1991.

23. Sibai BH, Anderson GD, Spinnato JA, Shaver OC : Plasma volume findings in patients with mild pregnancy induced hypertension. Am J Obstet Gynecol, 147:16-19, 1983.

24. Sumioki H, Shimokawa H, Miyamoto S, et al : Circadian variations of plasma atrial natriuretic peptide infour types of hypertensive disorder during pregnancy. Br J Obstet Gynaecol, 96:922-927, 1989.

25. Thomsen JK, Storm TL, Thomsborg G, et al : Atrial natriuretic peptide concentrations in preeclampsia. Br Med J, 294:1508-1510, 1987.

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