Physiology

LEVELS OF PLASMA ATRIAL NATRIURETIC PEPTIDE AND PLASMA RENIN ACTIVITY, AND THE RATIO BETWEEN THEM DURING NORMAL AND PREECLAMPTIC PREGNANCIES

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SUMMARY: To clarify the possible role of atrial natriuretic peptide (ANP) and plasma renin activity (PRA) in the pathophysiology of preeclampsia, and to evaluate the relationship between ANP and PRA in normal and preeclamptic pregnancies, we simultaneously measured ANP and PRA levels, and also determined ANP/PRA ratios in both normal pregnants (n=8) and preeclamptic patients (n=8) within their third trimesters. In the normal and preeclamptic pregnant women, mean (±SE) plasma ANP values were 25.48 ± 5.52 and 36.27 ± 6.70 pg/ml; and mean (±SE) PRA values were 2.70 ± 0.56 and 3.21 ± 1.09 ng/ml/h, respectively. The higher plasma ANP and PRA values in the preeclamptics were found to be non-significant. Mean (±SE) ANP/PRA ratio in the preeclamptic group was determined to be higher than that in normal pregnancy, the values being 23.0 ± 8.41 pg/ml and 14.05 ± 4.16 ng/ml/h respectively; this difference between the two groups was also found to be 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 in preeclampsia following increased PRA levels, which otherwise would trigger release of angiotensin II and aldosterone further and hence cause vasoconstriction and sodium retention to be more augmented.

Key Words: Atrial natriuretic peptide, plasma renin activity, pregnancy, preeclampsia.

INTRODUCTION

In normal pregnancy there is approximately 50 percent increase in the total extra cellular fluid and blood volumes, which are the results of approximately 900 mmol sodium retention (3, 27). The degree of plasma volume expansion in normal pregnancy is significantly and positively correlated with fetal birth weight (3). There also exists profound peripheral arterial vasodilatations in normal pregnancy, which leads to a condition 'sensed' as an under fill state, despite volume expansion to this degree (27). In preeclampsia, much research documents relative hypovolemia in comparison with normal pregnancy (3,10,14, 28), 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 (3). 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 (3).

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 (6,18). 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 (2, 9,10, 20, 21, 23, 31).

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Because many correlations do exist between ANP and the renin-angiotensin-aldosterone axis, and the two systems seem to operate in tandem to control volume homeostasis (17,18), we planned to simultaneously measure ANP and plasma renin activity (PRA) levels in both normal and preeclamptic pregnancies.

The aim of this study was to determine the relationship between ANP and PRA in normal pregnancy and in preeclampsia, and to examine how this relationship affects states of volume reduction and vasoconstriction, which are the prominent features in preeclampsia (3).

MATERIAL AND METHODS

Eight 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. Eight 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 39 years, and no evidence of renal and/or cardiovascular disorders were 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 (7), 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 pregnants 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 those 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.

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

Patient No	Age (years)	Weight (kg)	Parity	Abortus	Gestational Age at the study (weeks)	Blood pressure* (mmHg)
1	39	68	5	1	28	160/90
2	28	85	0	2	39	140/100
3	31	65	2	2	35	170/110
4	39	110	5	2	36	150/100
5	21	75	0	0	37	150/100
6	33	110	3	0	34	160/110
7	36	69	3	0	32	180/120
8	29	65	0	1	28	170/85

* Blood pressures at time of sampling.

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

	Age (years)	Weight (kg)	Parity	Gestational Age at the study (weeks)	Blood pressure* (mmHg)	
					systolic	diastolic
Normal pregnancy (n=8)	24.63 ±1.89	69.13 ±1.14	0.50 ±0.27	35.75 ±0.90	117.50 ±3.13	75.0 ±1.89
Preeclampsia (n=8)	32.0 ±2.16	80.88 ±6.76	2.25 ±0.75	33.63 ±1.43	160.0 ±4.63	101.88 ±4.41
Total (n=16)	28.31 ±1.68	75.0 ±3.64	1.38 ±0.45	34.69 ±0.86	138.75 ±6.12	88.13 ±4.11

*Blood pressure at time of sampling.

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 study day, blood pressures were evaluated by the same examiner as described above, and simultaneously, venous blood samples were collected in prechilled 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 kallikrein 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. Repeated freeze-thaw cycles were avoided.

Angiotensin I coated-tube RIA was performed in two aliquots of the same sample, one incubated at 37°C for generation and one non-incubated; then, PRA (plasma renin activity) was calculated as ng angiotensin I generated/ml/h (Renctk P2721, Sorin Biomedica Diagnostic Division RIA kit, Italy). The PRA assay sensitivity was 0.13 ng/ml; intra-and interassay coefficients of variation were 7.5 and 7.7%, respectively.

Plasma ANP levels were also evaluated by RIA (ANP I^{125} RIA kit, Incstar Corp., US, 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 (13). To improve the accuracy of the assays, cartridge extraction methods have been developed for plasma to purify the samples prior to being assayed (16, 24). In our study, ANP was extracted from plasma with an octadecasilyl-silica (ODS-silica) mini-column (Sep-Pac C_{18}); then the ANP from each mini-column was eluted by adding 4% acetic acid in 86% ethanol, and the eluates were collected in polystyrene tubes (16,

22, 24). The eluates were evaporated to complete dryness in a 37°C water bath, using compressed nitrogen. ANP levels were evaluated in dried samples by RIA.

After determination of the plasma ANP and PRA levels, ANP/PRA ratios were also evaluated.

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

RESULTS

Table 3 shows the mean (±SE) values of plasma atrial natriuretic peptide, plasma renin activity and ANP/PRA ratio in the pregnant groups. In the normal and preeclamptic pregnant groups, mean plasma ANP values were 25.48±5.52 and 36.27±6.70 pg/ml, respectively. Mean PRA values in the normal and preeclamptic pregnant groups were 2.70±0.56 and 3.21±1.09 ng/ml/h, respectively. Although mean plasma ANP and PRA values of the preeclamptic pregnants were higher than those of the normal pregnants (Figure 1), these differences were found to be non-significant (p>0.05).

Table 3: Values of plasma ANP, PRA and ANP/PRA ratio in the pregnant groups (mean±SE).

Groups	ANP (pg/ml)	PRA (ng/ml/h)	ANP/PRA
Normal pregnancy (n=8)	25.48 ± 5.52	2.70 ± 0.56	14.05 ± 4.16
Preeclampsia (n=8)	36.27 ± 6.70	3.21 ± 1.09	23.0 ± 8.41

None of the differences between 2 groups were found to be statistically significant (p>0.05).

Figure 1: Mean values of ANP and PRA in normal pregnancy (NP) and preeclampsia (PE).

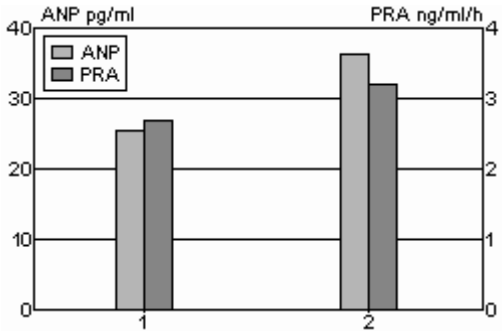
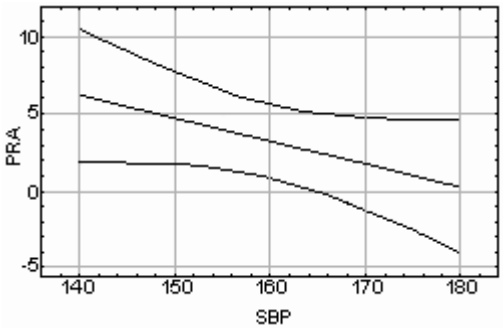


Figure 2: Increased systolic blood pressure (SBP) causes depression of PRA in the preeclamptic group (r =-0.6, p=0.09).

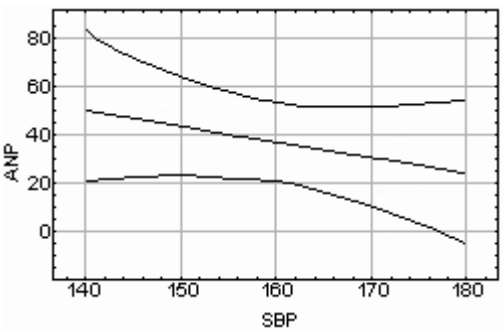


Mean ANP/PRA ratio in the preeclamptic group was higher than that of the normal pregnants (23.0±8.41 and 14.05±4.16, respectively). This difference between two groups, was also found to be non-significant (p>0.05).

The positive correlation between plasma ANP and PRA levels in the preeclamptic subjects was found to be slight (r=0.4), whereas the negative correlation between PRA levels and systolic blood pressure in the same group was found to be relatively strong (r=-0.6, Figure 2). Correlation between PRA levels and systolic blood pressure in the normal pregnants was not strong (r=-0.4).

There was however a slight, negative correlation between plasma ANP levels and systolic blood pressure in the preeclamptic pregnants (r=-0.5, Figure 3). The positive correlations between PRA levels and gestational week,

Figure 3: In the preeclamptic group, systolic blood pressure (SBP) decreases as plasma ANP level rises (r =-0.5, p=0.23).



and between plasma ANP levels and gestational week in the preeclamptic subjects were also found to be slight (r= 0.5 and 0.2, respectively). All correlations mentioned above were found to be statistically non-significant (p>0.05).

DISCUSSION

Plasma ANP and PRA

Mean plasma ANP value in the third trimester preeclamptic subjects was found to be higher than that of the normotensive pregnants (36.27±6.70 and 25.48±5.52, respectively), the difference between two groups was however non-significant (Table 3, Figure 1). Plasma ANP values in normal pregnants and preeclamptic subjects were found to range widely (from 15.47 to 62.3 and 15.88 to 66.86 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 (6,12). It has been reported in most studies that the mean plasma ANP value is significantly higher in preeclampsia than in normal pregnancy (2, 9,10, 20, 21, 23, 31).

Despite reduction of plasma volume in preeclampsia (3,10), this condition is associated with increased plasma concentrations of plasma ANP, which increase still further with the severity of the disease (32). 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 (8), since it was reported that pregnant women with proteinuria or edema but without hypertension had normal plasma ANP levels (15). 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 caused an increase in plasma ANP levels, and that mean pulmonary artery wedge pressure correlated with plasma ANP values (26). Carlsson (4) reported that although central venous pressure was within normal ranges in preeclampsia, mean pulmonary artery wedge pressure increased above the normal limit. This finding 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 a diminished glomerular filtration rate. ANP is cleared not only by kidneys, but also by the liver and skeletal muscle (5). 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 (8).

The mean PRA value in the preeclamptic subjects was found to be slightly higher than that of normal pregnants (3.21 and 2.70 ng/ml/h, respectively), the difference being non-significant (Table 3, Figure 1). In most studies, it has been reported that plasma renin activity in preeclamptic pregnancies decreases, whereas the value in normal pregnants increases significantly, when compared with its measurements in normal non-pregnant subjects (1,19, 29, 33). More recently, some authors have noted increments in both plasma renin activity and angiotensin levels in preeclampsia (7,11). Despite the increment in blood volume and extra cellular fluid volume, increased activity of the renin-angiotensin-aldosterone system is a characteristic of normal pregnancy, which is also associated with arterial vasodilatation. During normal pregnancy, expansion of intravascular space is so great that in spite of hypervolemia it causes a state of arterial under filling, which stimulates release of renin (3).

In the case of preeclampsia, there is early 'over-expansion' of the plasma volume followed by 'escape' from this positive sodium balance and consequent reduction of the plasma volume. Vasoconstriction is a dominant feature of preeclampsia, and plasma volume reduction is not appropriate for this vasoconstrictor state. Therefore, preeclamptic subjects 'sense' this reduced plasma volume, since sodium retention ensues as an expected homeostatic renal response (3).

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.

Endothelial damage leads to pathophysiologic events that characterize preeclampsia, with resultant release of endothelin, which causes renal blood flow to decrease (25, 27). So, decreased renal blood flow and 'sensation' of

reduced plasma volume in preeclamptic pregnancy may explain our finding that, mean plasma renin activity in preeclamptic patients is increased but not decreased. Increased PRA levels may in turn lead to vasoconstriction in preeclampsia, by triggering release of angiotensin II. This conclusion is supported by Furuhashi *et al.*, who reported that angiotensin II was slightly higher in preeclampsia than in normal pregnancy (11).

It's known that ANP produces marked and sustained suppression of both renal renin secretion and plasma renin levels (18). So, it is reported that increased plasma levels of ANP with simultaneous low levels of plasma renin may explain the inappropriate hypostimulation of renin secretion by hypovolemia in preeclamptic states (10). In our study, both mean plasma ANP and PRA values were found to be elevated non-significantly in preeclamptic subjects. We, therefore, conclude that increased ANP level in preeclampsia leads to suppression of PRA concentration, which other vise would be elevated significantly due to marked plasma volume reduction in preeclamptic subjects.

In contrast to Bond's results (2), in preeclampsia, we found a slight, positive correlation between plasma ANP and PRA levels (r=0.4) and this finding may indicate a compensatory mechanism that is triggered following the increased susceptibility of the vascular bed to angiotensin II in this hypertensive state (18). Since renin triggers the pathway that releases angiotensin II, this finding may also be attributed to the balance maintained between natriuretic and anti-natriuretic, and/or between vasodilator and vasoconstrictor factors in preeclamptic pregnancy.

The negative correlations that we determined between PRA levels and systolic blood pressure in both groups may indicate that increased blood pressure causing depression of renin release operates well in both normal and preeclamptic pregnancies, the correlation being relatively stronger in the hypertensive pregnants (Figure 2; r=-0.6 in the preeclamptics, and -0.4 in normotensive pregnants).

The positive correlations observed by us in this study between plasma PRA and ANP levels and gestational age in preeclampsia may indicate increased release of ANP and renin in relation to gestational age in this hypertensive state. The higher positive correlation between PRA levels and gestational week (r=0.5), than that between plasma ANP levels and gestational age (r=0.2) in preeclampsia may indicate that release of vasoconstrictor and/or anti-natriuretic factors increase in excess of vasodilators and/or natriuretics in relation to gestational age, leading to augmentation of vasoconstriction and sodium retention as preeclamptic pregnancy advances.

ANP/PRA ratio

We determined that mean ANP/PRA value in the preeclamptic subjects was higher than that of the normal pregnants (23.0±8.41 and 14.05±4.16, respectively), the difference between two groups being non-significant (Table 3). From this result, there emerges a paradox that preeclampsia is associated with higher ANP/PRA ratios and lower intravascular volumes, since ANP secretion is known to increase in response to plasma expansion (6,12); but higher ANP/PRA ratio may explain volume reduction characteristic of preeclampsia, by causing both a sodium wastage and failure of water-and sodium-saving factors to expand maternal volume adequately. 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 (18). Therefore, these data suggest a compensatory role of ANP in the prevention of blood pressure increase, which is further supported by our another finding that a slight, negative correlation exists between plasma ANP levels and systolic blood pressure in the preeclamptic group (r=-0.5, Figure 3). In contrast to our finding, Fievet (10) has reported a positive correlation between plasma ANP and mean arterial pressure in hypertensive pregnant women.

Stratta *et al.* (30) reported low aldosterone/ANP ratio in preeclampsia, and this finding supports our result related to ANP/PRA ratio; since renin triggers the axis that leads to release of aldosterone, both findings indicate that there may be failure of sodium retaining factors to expand maternal volume efficiently in preeclampsia. There are many correlations between ANP and the renin-angiotensin-aldosterone axis, and these two systems seem to work in tandem to control volume homeostasis (17,18). Therefore, ANP/PRA ratio, which indicates the balance between PRA and ANP, may be a more useful index than the absolute concentrations of these substances, in determining sodium homeostasis during normal pregnancy and preeclampsia.

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