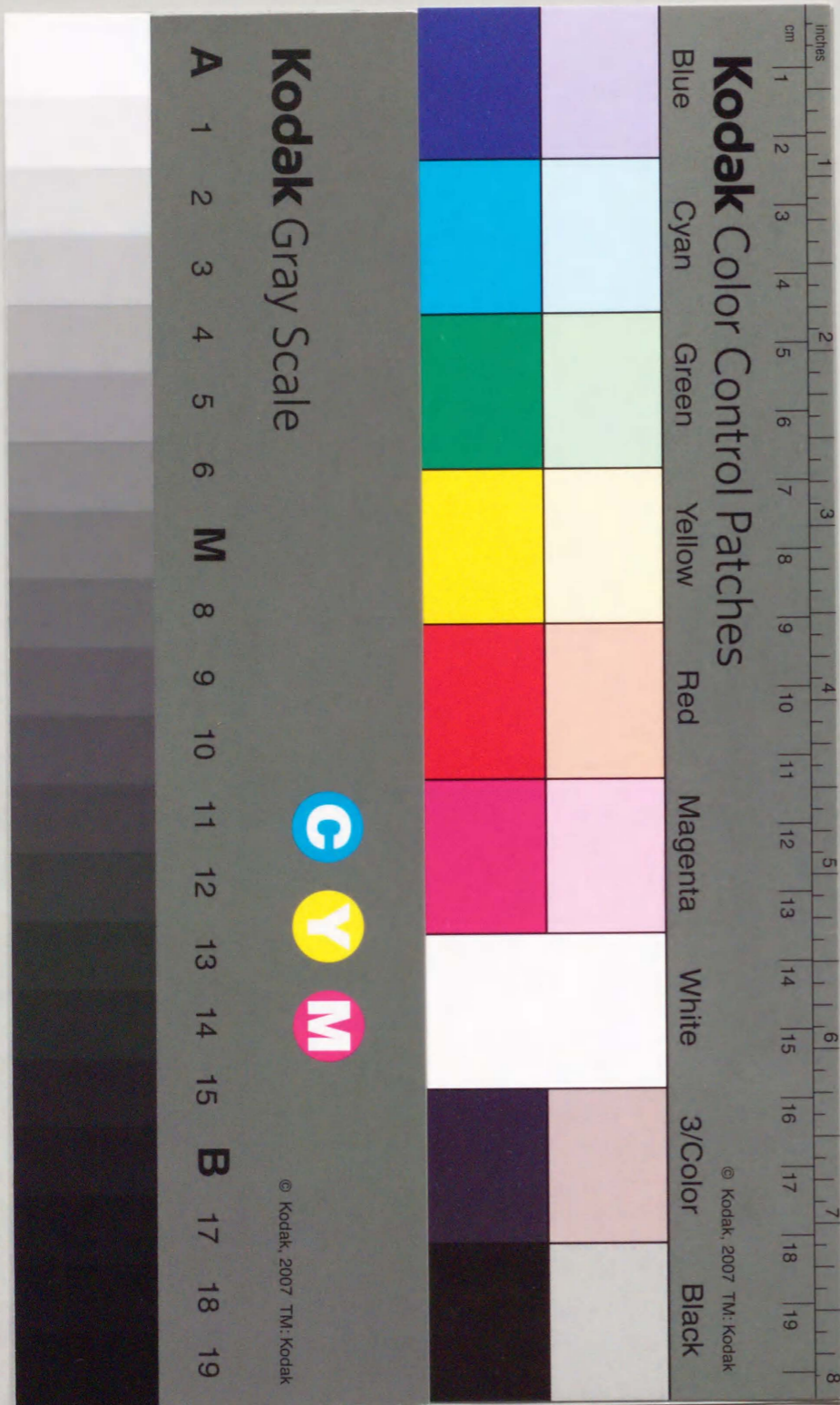


Circadian rhythm of plasma atrial natriuretic peptide, aldosterone, and blood pressure during the third trimester in normal and preeclamptic pregnancies

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Circadian rhythm of plasma atrial natriuretic peptide, aldosterone, and blood pressure during the third trimester in normal and preeclamptic pregnancies

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The influence of pregnancy on circadian variations of plasma atrial natriuretic peptide and aldosterone was studied. In those women with normal pregnancies, the mean 24-hour values of atrial natriuretic peptide and aldosterone increased, compared with the levels in normal nonpregnant subjects. In cases of severe preeclampsia, levels of atrial natriuretic peptide were significantly higher than in the other subjects, but aldosterone levels decreased to nearly those seen in the nonpregnant subjects. Atrial natriuretic peptide did not establish a rhythm in normal nonpregnant and pregnant subjects, but in the studies of aldosterone levels, a clear circadian rhythm was evident. In severe cases of preeclampsia, atrial natriuretic peptide established a circadian rhythm similar to that of blood pressure, and the circadian rhythm of aldosterone disappeared. The main characteristic of the rhythm in atrial natriuretic peptide and blood pressure in women showing preeclamptic signs is that the acrophase occurred at midnight. This evidence suggests that in women with symptoms of preeclampsia the load to the atria increases at midnight. (AM J OBSTET GYNECOL 1988;158:393-9.)

Key words: Atrial natriuretic peptide, aldosterone, preeclampsia, circadian rhythm

Atrial natriuretic peptide has potent natriuretic, diuretic, and smooth muscle relaxant properties and has been isolated from human atrial tissue.¹ The role of atrial natriuretic peptide in physiologic and pathophysiologic states in mammals, including human beings, has been investigated.

It was reported that synthetic atrial natriuretic peptide injection induced natriuresis, a decrease in the plasma aldosterone level, and a decrease in blood pressure.^{2,3} However, the role of endogenous atrial natriuretic peptide in humans is debatable. Apparently there has been no report on changes in plasma atrial natriuretic peptide values and the role of atrial natriuretic peptide in hemodynamic changes occurring during pregnancy.

We measured the concentration of plasma atrial natriuretic peptide and aldosterone in normal and preeclamptic pregnant Japanese women to assess the significance of endogenous atrial natriuretic peptide in preeclamptic states.

Material and methods

Five normal nonpregnant women and 25 normal pregnant subjects were studied after 28 weeks of gestation, and six primiparous women with severe preeclampsia were also studied. Their ages ranged from 22 to 35 years, and no evidence of renal or cardiovascular diseases was present. Informed consent was obtained from each subject before initiation of the study.

Group 1 consisted of five normal nonpregnant subjects; group 2, six normal pregnant subjects between 28 and 31 weeks of gestation; group 3, seven normal pregnant subjects between 32 and 35 weeks of gestation; group 4, 12 normal pregnant subjects between 36 and 39 weeks of gestation; group 5, six primiparous, severely preeclamptic women between 30 and 35 weeks of gestation. Clinical data on these women with severe preeclampsia are shown in Table I. The diagnosis of preeclampsia was determined by means of the Criteria of the Committee on Preeclampsia, Japan Society of Obstetrics and Gynecology.⁴ In the present study, all women with preeclampsia had a blood pressure of $\geq 160/110$ mm Hg.

All of the women had been admitted to Kyushu University Hospital at least 2 days before the study was done. The normal nonpregnant and pregnant subjects were prescribed a diet containing approximately 170 mEq/day of sodium, and the women with severe preeclampsia were given about 120 mEq/day of sodium.

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Table I. Clinical data on the six women with severe preeclampsia

Patient No.	Gestational age at time of sampling (wk)	Gestational age at time of onset (wk)	Clinical data				
			Age (yr)	Blood pressure (mm Hg)	Proteinuria (gm/day)	Edema	Convulsion
1	30	28	24	162/112	4	Pos.	Absent
2	35	32	26	170/110	5	Neg.	Absent
3	31	30	29	164/112	4	Neg.	Absent
4	33	31	30	160/118	3	Neg.	Absent
5	34	33	30	176/110	5	Pos.	Absent
6	31	28	24	166/110	4	Pos.	Absent

Pos.: Positive. Neg.: negative.

Table II. Plasma atrial natriuretic peptide values at each hour, mean 24-hour values, and percent deviation from mean 24-hour values

	Mean 24 hr value (pg/ml)	Deviation (%)	Plasma atrial natriuretic peptide value (pg/ml)					
			2 AM	6 AM	10 AM	2 PM	6 PM	10 PM
Group 1 (n = 5)	43.7 ± 1.6	15.8 ± 10.5	40.5 ± 7.0	42.8 ± 7.0	44.3 ± 5.9	51.3 ± 5.8	40.0 ± 4.1	43.5 ± 6.7
Group 2 (n = 6)	90.9 ± 5.9	13.3 ± 18.4	76.2 ± 14.3	89.0 ± 9.7	109.9 ± 11.6	86.7 ± 14.2	83.6 ± 10.2	100.2 ± 10.6
Group 3 (n = 7)	73.3 ± 2.9	21.7 ± 11.3	73.5 ± 14.6	74.2 ± 9.3	66.8 ± 5.2	61.5 ± 5.1	84.3 ± 11.2	79.5 ± 9.5
Group 4 (n = 12)	98.2 ± 3.5	29.1 ± 10.2	119.0 ± 18.0	103.7 ± 10.2	80.7 ± 9.0	92.0 ± 14.0	93.1 ± 12.1	100.5 ± 14.0
Group 5 (n = 5)	243.9 ± 5.8	42.1 ± 6.8	275.9 ± 35.2	238.8 ± 24.3	176.5 ± 15.4	218.9 ± 39.8	267.6 ± 19.7	285.8 ± 24.6

Group 1: Nonpregnant women; group 2: pregnant women between 28 and 31 weeks' gestation; group 3: pregnant women between 32 and 35 weeks' gestation; group 4: pregnant women between 36 and 39 weeks' gestation; group 5: women with severe preeclampsia.

Breakfast was served at 8 AM, lunch at 12 noon, and dinner at 4:30 PM. All subjects remained in bed except to urinate and defecate and they slept between 10 PM and 6 AM. No drugs were ingested before and/or during the study.

The same examiner (S. M.) measured the blood pressure every 4 hours, at 6 AM, 10 AM, 2 PM, 6 PM, 10 PM, and 2 AM, with a manual sphygmomanometer at the right brachial artery and the woman lying in the left recumbent position for ≥15 minutes. Simultaneously, venous blood samples were collected in chilled tubes containing 2N ethylenediaminetetra-acetic acid and the 2500 kallikrein inhibitor unit Trasylol (Bayer, Leverkusen, West Germany). The plasma was immediately separated by centrifuge at 4°C and stored at -70°C until assay.

Plasma human atrial natriuretic peptide was measured by radioimmunoassay as described,⁵ except that human atrial natriuretic peptide was extracted from plasma (2.0 ml) with an ODS-silica minicolumn (Sep-Pac C 18, Waters Associates Inc., Milford, Mass.), and eluted with 60% (vol/vol) acetonitrile/-0.1N acetic

acid. The recovery rate of human atrial natriuretic peptide labeled with iodine 125 and added to plasma was 70.8% ± 5.3% (mean ± SD; n = 15). A radioimmunoassay of human atrial natriuretic peptide was done with synthetic human atrial natriuretic peptide (Peptide Institute Inc., Osaka, Japan) used as an assay standard along with anti-human atrial natriuretic peptide antiserum and ¹²⁵I-labeled atrial natriuretic peptide (Amersham International Ltd., London, England) as a tracer. A sample (100 μl) or a standard (100 μl) was incubated with antibody (100 μl) for 48 hours at 4°C before the addition of the tracer. The assay mixture contained ¹²⁵I-labeled human atrial natriuretic peptide (3000 cpm), anti-human atrial natriuretic peptide antiserum, and the plasma extract in 0.25 ml of radioimmunoassay buffer (0.05 mol/L phosphate buffer, pH 7.4, containing 0.1% bovine serum albumin, 0.05% sodium azide, 0.1% Triton X-100, 0.08 mol/L sodium chloride, and 0.025 mol/L 2N ethylenediaminetetra-acetic acid). Antibody-bound and free human atrial natriuretic peptide were separated with the double-antibody method. The assay sensitivity was 12.5 pg/tube (100 μl). The

Table III. Plasma aldosterone values at each hour, 24-hour values, and percent deviation from mean 24-hour values

	Mean 24 hr value (pg/ml)	Deviation (%)	Plasma aldosterone value (ng/ml)					
			2 AM	6 AM	10 AM	2 PM	6 PM	10 PM
Group 1 (n = 5)	68.7 ± 1.7	44.0 ± 7.0	54.7 ± 12.0	75.7 ± 12.1	80.0 ± 14.9	79.0 ± 16.2	70.0 ± 13.2	52.6 ± 11.0
Group 2 (n = 6)	97.6 ± 1.5	22.3 ± 4.5	95.4 ± 17.9	110.9 ± 18.0	103.5 ± 17.0	101.0 ± 13.1	89.7 ± 15.9	87.0 ± 16.6
Group 3 (n = 7)	140.4 ± 1.9	26.3 ± 3.8	139.8 ± 21.4	149.4 ± 20.4	162.7 ± 12.3	141.6 ± 16.4	124.7 ± 10.6	124.1 ± 10.7
Group 4 (n = 12)	143.5 ± 2.1	14.2 ± 4.1	129.1 ± 11.7	147.0 ± 13.5	150.3 ± 14.0	153.6 ± 11.5	141.0 ± 12.1	139.5 ± 10.3
Group 5 (n = 5)	76.1 ± 0.9	3.5 ± 3.5	75.7 ± 9.6	78.9 ± 11.7	76.8 ± 9.2	73.6 ± 10.3	77.4 ± 10.3	74.0 ± 8.8

Group 1: Nonpregnant women; group 2: pregnant women between 28 and 31 weeks' gestation; group 3: pregnant women between 32 and 35 weeks' gestation; group 4: pregnant women between 36 and 39 weeks' gestation; group 5: women with severe preeclampsia.

intra-assay and interassay coefficients of variation were 6.9% (n = 10) and 8.3% (n = 12), respectively. The dilution curve of plasma extracts paralleled that of the control standards. Radioimmunoassay of aldosterone was performed with commercial kits (Aldoc TK 125, Midori Juji, Tokyo, Japan).

The nadir-to-peak excursions of plasma atrial natriuretic peptide and aldosterone were expressed as the percentage of deviation from the mean 24-hour values. Cosinor analysis⁶ was used to evaluate circadian rhythmicity. A *p* value of <0.1 was regarded as being statistically significant. Statistical analysis of mean 24-hour values was performed with Student's *t* test. The values of plasma atrial natriuretic peptide and aldosterone were expressed as the mean ± SEM.

Results

Chronologic changes of plasma human atrial natriuretic peptide and aldosterone during pregnancy. Tables II and III show the 24-hour mean values and percent deviations of plasma atrial natriuretic peptide and aldosterone in all groups. In groups 1, 2, 3, and 4, plasma atrial natriuretic peptide values were 43.7 ± 1.6, 90.9 ± 5.9, 73.3 ± 2.9, and 98.2 ± 3.5 pg/ml, respectively. The mean 24-hour value of group 1 (nonpregnant subjects) was significantly lower than that in groups 2, 3, and 4 (normal pregnant subjects) (*p* < 0.05, *p* < 0.05, and *p* < 0.01, respectively). However, no significant differences were noted between groups 2, 3, and 4. In group 5 (with severe preeclampsia), the plasma atrial natriuretic peptide level (243.9 ± 5.8 pg/ml) was significantly higher than that in other groups (*p* < 0.01).

In groups 1, 2, 3, and 4, plasma aldosterone values were 68.7 ± 1.7, 97.6 ± 1.5, 140.4 ± 1.9, and 143.5 ± 2.1 pg/ml, respectively. There was no significant difference between groups 1 and 2, but plasma aldoste-

rone levels in groups 3 and 4 were higher than in groups 1 and 2 (*p* < 0.01). In group 5, the plasma aldosterone value was 76.1 ± 0.9 pg/ml. No significant differences were noted between groups 1, 2, and 5. However, the plasma aldosterone level in group 5 was significantly lower than that in groups 3 and 4 (*p* < 0.01).

Circadian rhythm of plasma human atrial natriuretic peptide, aldosterone, and blood pressure. Plasma atrial natriuretic peptide and aldosterone values at each sampling are shown in Tables II and III. Cosinor analysis of plasma atrial natriuretic peptide did not confirm a clear circadian rhythm in groups 1, 2, 3, and 4. The nadir-to-peak excursions were much the same in these groups. On the other hand, cosinor analysis confirmed a significant circadian rhythm in group 5 (*p* < 0.02), with the acrophase (the theoretical time the peak value is reached) occurring at 11 PM and the nadir value at 10 AM. Plasma atrial natriuretic peptide excursions were clearly marked (Fig. 1). Cosinor analysis of plasma aldosterone levels confirmed a clear circadian rhythm in groups 1, 2, 3, and 4 (*p* < 0.02, *p* < 0.04, *p* < 0.02, and *p* < 0.1, respectively) (Fig. 2) and demonstrated that the acrophase in groups 1 and 4 was later than that in groups 2 and 3 (*p* < 0.05). The nadir-to-peak excursions of plasma aldosterone levels were significantly decreased in group 2 when compared with those in group 1 (*p* < 0.02). In all normal pregnant groups, the nadir-to-peak excursions of plasma aldosterone levels tended to decrease when compared with those in group 1. On the other hand, circadian rhythm was not confirmed by cosinor analysis in group 5. The nadir-to-peak excursion in group 5 was significantly inhibited when compared with that in groups 2 and 3 (*p* < 0.02 and *p* < 0.01). Therefore, circadian variation appeared to be flat in women with severe preeclampsia.

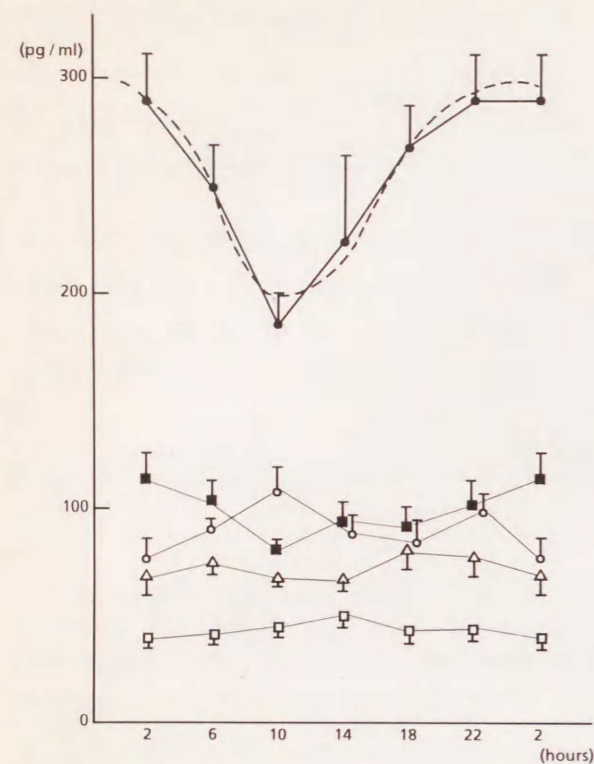


Fig. 1. Diurnal variations of plasma atrial natriuretic peptide values. *Solid line* shows measured values (mean \pm SEM). *Dotted line* shows theoretical values obtained by cosinor analysis. \square : Nonpregnant women; \circ : pregnant women between 28 and 31 weeks' gestation; \triangle : pregnant women between 32 and 35 weeks' gestation; \blacksquare : pregnant women between 36 and 39 weeks' gestation; \bullet : women with severe preeclampsia.

Figs. 3 and 4 show the circadian variations of systolic blood pressure and diastolic blood pressure in all groups. The values were expressed as the mean percent deviation from the mean 24-hour values. As shown in Fig. 3, systolic blood pressure reached peak values at 6 PM and fell to nadir values at 2 AM in groups 2, 3, and 4. The pattern of blood pressure changes in group 1 was similar to that in groups 2, 3, and 4, but the peak value was reached at 10 AM. On the other hand, in the circadian variations of systolic blood pressure in group 5, the peak values occurred at 2 AM and the nadir values at 2 PM. Fig. 4 shows the circadian variations of diastolic blood pressure in all groups. The patterns of circadian variations were similar to those of systolic blood pressure in all groups. The circadian variations of systolic blood pressure and diastolic blood pressure in group 5 were opposite those values found in the other groups.

Comment

Chronologic changes of plasma human atrial natriuretic peptide and aldosterone. Plasma atrial natriuretic peptide values in subjects in the third trimester

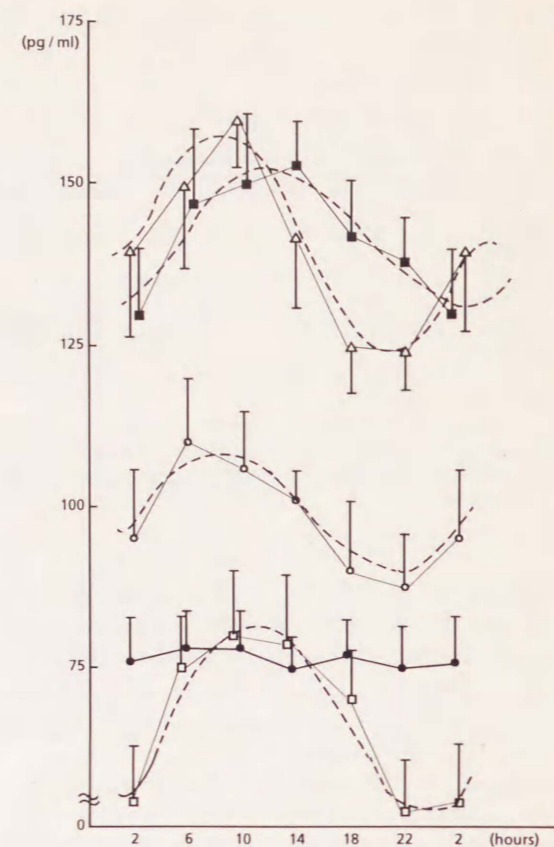


Fig. 2. Diurnal variations of plasma aldosterone values. *Solid line* shows measured values (mean \pm SEM). *Dotted line* shows theoretical values obtained by cosinor analysis. \square : Nonpregnant women; \circ : pregnant women between 28 and 31 weeks' gestation; \triangle : pregnant women between 32 and 35 weeks' gestation; \blacksquare : pregnant women between 36 and 39 weeks' gestation; \bullet : women with severe preeclampsia.

of a normal pregnancy increased significantly when compared with findings in normal nonpregnant subjects. Plasma atrial natriuretic peptide values in normal nonpregnant subjects were reported to range widely, from 18 to 63 pg/ml.⁷ In normal nonpregnant subjects, plasma atrial natriuretic peptide values reported from some laboratories were slightly lower than those in our study, these lower values perhaps being related to salt intake, sampling time, and/or posture of the patient at the time of blood sampling. It has been reported that release of atrial natriuretic peptide is stimulated by atrial distension or stretch and that plasma atrial natriuretic peptide values increase in response to short-term or long-term plasma expansion.⁸ During a normal pregnancy, the plasma volume increases markedly to approximately 45% above the levels in nonpregnant women.⁹ The increase of plasma atrial natriuretic peptide values in normal pregnant subjects may be caused mainly by plasma expansion. However, plasma atrial natriuretic peptide values in women with severe pre-

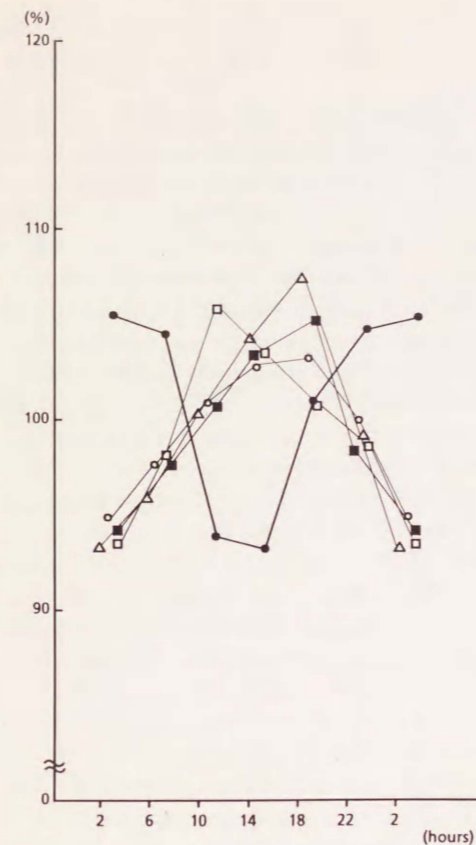


Fig. 3. Diurnal variations of systolic blood pressure. Values were expressed as the mean percent deviation from the mean 24-hour values. \square : Nonpregnant women; \circ : pregnant women between 28 and 31 weeks' gestation; \triangle : pregnant women between 32 and 35 weeks' gestation; \blacksquare : pregnant women between 36 and 39 weeks' gestation; \bullet : women with severe preeclampsia.

eclampsia were significantly higher than those found in the normal pregnant subjects, although the plasma volume in women with severe preeclampsia was found to decrease significantly when compared with the findings in normal pregnant women.⁹ Therefore, this phenomenon in preeclampsia cannot be explained by changes of plasma volume. In cases of preeclampsia, hypertension is one of the symptoms that is most difficult to manage, and the main pathophysiologic cause is generalized vasoconstriction. It has been reported that plasma atrial natriuretic peptide values in uncomplicated essential hypertension were within normal ranges, regardless of the plasma renin concentration.¹⁰ However, Sato et al.¹¹ reported that an increase in plasma atrial natriuretic peptide values was caused by an increase in mean pulmonary artery wedge pressure and that mean pulmonary artery wedge pressure correlated with plasma atrial natriuretic peptide values. In conditions of preeclampsia, the central venous pressure was within normal ranges, but mean pulmonary artery wedge pressure increased beyond the normal limit,

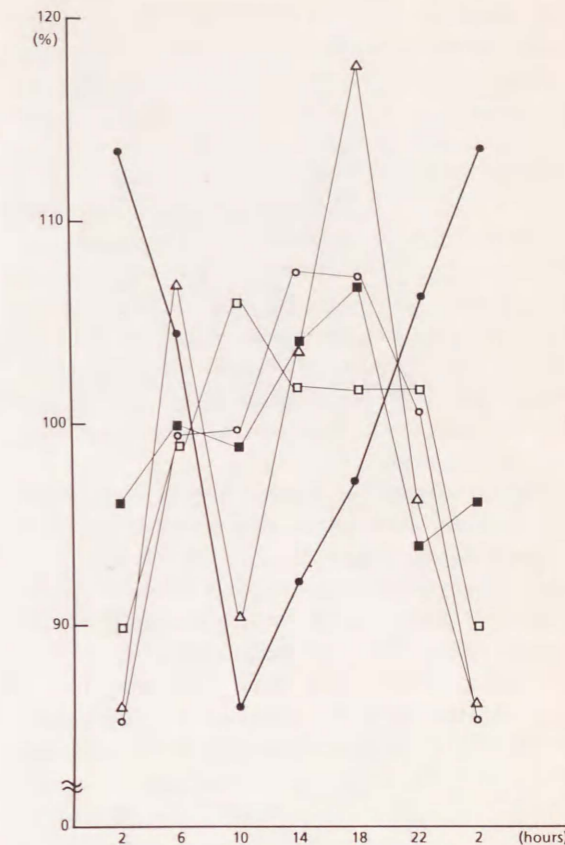


Fig. 4. Diurnal variations of diastolic blood pressure. Values were expressed as the mean percent deviation from the mean 24-hour values. \square : Nonpregnant women; \circ : pregnant women between 28 and 31 weeks' gestation; \triangle : pregnant women between 32 and 35 weeks' gestation; \blacksquare : pregnant women between 36 and 39 weeks' gestation; \bullet : women with severe preeclampsia.

probably because of generalized vasoconstriction.¹² This evidence indicates that an increase in the plasma atrial natriuretic peptide values in women with severe preeclampsia may be caused by the distension or stretching of the left atrium and suggests that the stretching may reflect a state of generalized vasoconstriction. The mechanism of increased plasma atrial natriuretic peptide values differs between those women with normal pregnancies and those with preeclamptic symptoms.

Plasma aldosterone values increased significantly in normal pregnant subjects in the third trimester of pregnancy when compared with findings in normal nonpregnant subjects. On the other hand, plasma aldosterone values in women with severe preeclampsia decreased almost to the level found in normal nonpregnant subjects. These results are compatible with reported data.¹³

Waldhausl et al.² and Weidmann et al.³ reported that the injection of synthetic atrial natriuretic peptide in human subjects led to a decrease in plasma aldosterone

values. However, the level of plasma atrial natriuretic peptide obtained by synthetic atrial natriuretic peptide injection may be beyond the normal limits in the physiologic state of human subjects. The maximum values of plasma atrial natriuretic peptide in the study of Weidmann et al.³ are markedly higher than values in women with severe preeclampsia in the present study. The minimum values of plasma atrial natriuretic peptide that can inhibit aldosterone synthesis have not been clearly defined. Therefore, it cannot be confirmed that low aldosterone values are caused by high plasma atrial natriuretic peptide values in women with preeclampsia. The role of endogenous atrial natriuretic peptide with regard to aldosterone synthesis in preeclampsia requires further study.

Circadian rhythm of plasma human atrial natriuretic peptide, aldosterone, and blood pressure. In our study, plasma atrial natriuretic peptide did not establish a clear circadian rhythm, and the nadir-to-peak excursion of plasma atrial natriuretic peptide did not change in either normal nonpregnant women or pregnant women. On the other hand, cosinor analysis of plasma aldosterone levels confirmed a definite circadian rhythm in normal nonpregnant and pregnant women, and the nadir-to-peak excursion decreased gradually through the third trimester of pregnancy. The circadian rhythm of plasma aldosterone may be controlled by adrenocorticotropic hormone secretion rhythm because the circadian rhythm of plasma aldosterone is similar to that of plasma cortisol.¹⁴ The pregnancy-associated blunting of the nadir-to-peak excursion of plasma cortisol has been explained by autonomous placental secretion of an adrenocorticotropic hormone-like substance.¹⁵ The blunting of nadir-to-peak excursion in plasma aldosterone rhythm may also be caused by the same mechanism in normal pregnant women. Since the diurnal variation of plasma atrial natriuretic peptide (unlike plasma aldosterone) did not establish a clear circadian rhythm, atrial natriuretic peptide secretion is probably little influenced by aldosterone and adrenocorticotropic hormone secretion. In addition, the evidence that plasma atrial natriuretic peptide values did not change throughout the day indicates that right and left atrial pressure remained fairly stable in the normal nonpregnant and pregnant women.

In cases of severe preeclampsia, the excursion of the circadian rhythm of plasma aldosterone decreased significantly and revealed a flat pattern. Kauppila et al.¹⁶ reported that the response of the adrenal gland to synthetic adrenocorticotropic hormone was suppressed significantly in women with preeclampsia when compared with that in normal nonpregnant and pregnant women. The absence of or a significant decrease in a circadian variation of plasma aldosterone in women

with preeclampsia may be caused by a decreased response of the adrenal gland to adrenocorticotropic hormone.

On the other hand, the circadian variation of plasma atrial natriuretic peptide established a clear circadian rhythm in women with severe preeclampsia. The circadian rhythm of plasma atrial natriuretic peptide was similar to that of blood pressure in the women with preeclampsia. All of these women with preeclampsia had nocturnal hypertension, and the circadian rhythm of blood pressure found in them was the opposite of the rhythm of normal nonpregnant and pregnant subjects in this study. This finding would suggest that, in those women with preeclampsia, the right, left, or both atrial walls distended or stretched at the same time the blood pressure rose significantly. Two pathophysiologic changes may be considered. The first is distension or stretching of the atria caused by increased afterload resulting from enhancement of generalized vasoconstriction. The second is distension or stretching of the atria caused by increased venous blood return or increased blood volume as a result of the shift of extracellular fluid from extravascular to intravascular compartments. It could not be confirmed by this study which pathophysiologic process occurred at midnight in the preeclamptic women. However, the load to the atria did increase significantly and rapidly at midnight, a time when the blood pressure significantly increased in the women with preeclampsia.

In conclusion, the mean 24-hour atrial natriuretic peptide values and circadian rhythm of plasma atrial natriuretic peptide reflect the physiologic and pathophysiologic hemodynamic process in normal and preeclamptic pregnancies. The markedly increased mean 24-hour atrial natriuretic peptide values may compensate for the generalized vasoconstriction, and the increase of plasma atrial natriuretic peptide values at midnight may reflect an increase of the load to the atria in the preeclamptic women.

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