Changes of Plasma Atrial Natriuretic Peptide (hANP) in Different Types of Hypertensive Disorders of Pregnancy

Zafirovska GK[1], Maleska TV[2], Bogdanovska VS[1], Lozance ALj[1], Gerasimovska DB[1]
Dept. of Nephrology[1], Dept. of Physiology[2], Faculty of Medicine, Skopje

Introduction

Hypertensive disorders are common complication during gestation occurring in 6 to 8 percent of pregnancies and remain a major cause of morbidity and mortality for both mother and foetus (1,2). Pregnancy is associated with significant hemodynamic, cardiovascular and renal changes to meet the metabolic needs of both mother and foetus (3-9). Human atrial natriuretic peptide (hANP) is released from cardiac atria in response to a variety of stimuli and has potent effects on both cardiovascular and renal systems (10,11). Possible alterations in ANP release during normal and hypertensive pregnancy have potentially significant role in its pathogenesis. (12-14).

The aims of this study were to follow changes of plasma ANP (pg/ml), and to determine relationship with GFR (ml/min), urinary excretion of sodium (UENa) and hematocrit (HCT) in different types of hypertensive disorders of pregnancy and to clarify the possible role in the pathophysiology of pregnancy induced hypertension.

Subjects and Methods

A prospective, longitudinal study was conducted on 85 pregnant women matched for age and body hight. The inclusion criterion was 8-13wg or less. PE was defined according to the criteria by Dekker and Sibai (14). All women were enrolled in the study either as normotensive or as preexisting hypertension. After termination of pregnancy four groups were formed if the criteria for classification (14,15) were fulfilled: normotensive pregnancy - Gr. NP, n=38, patients with preeclampsia - Gr. PE (n=17), preexisting hypertension without superimposed preeclampsia (gr. CH, n=17) and preeclampsia superimposed on CH (SPE, n=13).

GFR was calculated from the Cockroft & Gold formula. Venous blood samples for plasma ANP (pg/ml) were obtained at the end of the 8^{th} -13^{th}, 18^{th}, 23^{rd}, 28^{th}, 32^{nd} and 36^{th} wg when ambulatory 24-h. BP monitoring was performed and 24-hours urine samples were collected. Plasma hANP was measured by using specific radioimmunoassay kit (Amersham) after extraction from 1ml of plasma with minicolumns (16).

The values of all investigated parameters are expressed as mean ± SD. Standarad statistical tests were used. The level of significance was $p<0.05$. To analyse the relation of a dependant variable with a group of selected independent variables, the model of forced Multiple Regression Analysis (MRA) was used.

Results

The clinical characteristics of patients are shown on table 1. The groups differed for body weight and consequently for BMI ($p<0.05$ for all hypertensive groups vs. NT group). The concentrations of h-ANP in 8^{th} wg were higher in all groups compared to NT group (84.33±9.34 vs 110.44±23.96, 116.78±47.76 and 104.80±26.77, $p\leq0.05$), being the highest in SPE group. The points at which changes that distinguished the behavior of the groups with and without PE started were 23^{rd} wg and 28^{th} wg, reaching the maximum at 32^{th} -36^{th} wg (Figure 1).

Table 1. Clinical characteristics of patients

	Group NT	Group CH	Group SPE	Group PE	p
Age, yrs	28.6±5.2	31.1±5.2	32.4±5.1	29.3±5.4	NS
Hight, cm	162.9±6.8	162.9±6.8	162.2±8.2	162.0±6.8	NS
Weight, kg	68.9±13.0	79.4±13.0	75.8±16.6	73.9±17.2	*
BMI, kg/m^2	26.1±4.7	29.5±4.7	28.7±4.8	28.1±6.0	*
MAP24h, mmHg	86.0±5.2	86.0±5.2	100.6±8.6	86.6±5.7	**/ #

NT-normotensive; CH-chronic hypertension; SPE–preeclampsia superimposed on chronic hypertension, PE-preeclampsia
* $p<0.05$ all hypertensive groups versus NT
** Group SPE versus all other groups
\# Blood pressure values controlled with antihypertensive drugs in groups with preexisting hypertension

Correspondence to: Zafirovska Katica, Vasil GFjorgov 33a-2, Skopje 1000, Macedonia, tel 389-2-3136-516
Fax 389-2-3114-093, e-mail kzafir@sonet.com.mk

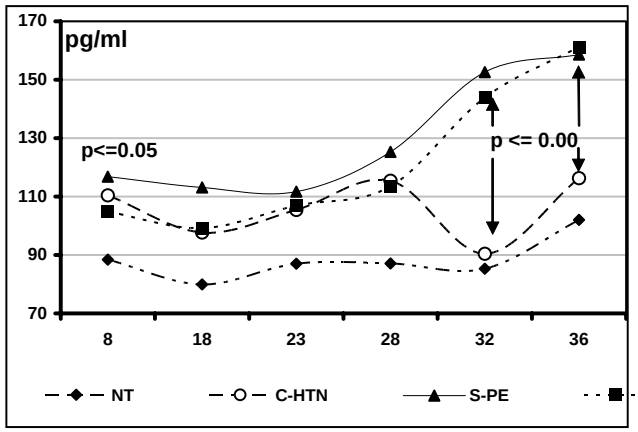
ANP in the NT group decreased non significantly from 8th till 32nd wg, than increased to 102.0±17.4 in the 36th, p≤0.008 vs. any previous level by wg. The same pattern, but on a higher level of ANP was demonstrated by the CH group: 110.44±24 in 8th wg, p=0.02, than maintained plateau till 32th wg, and decreased again to 90.4±21.2 (p≤0.01 vs 8th, 28th and 36th wg). In 32nd wg ANP did not differ between NT and CH groups. In CH group ANP increased in 36thwg to 116.3±16 (p=0.04 vs NT). Changes of hANP in the groups with preeclampsia followed identical pattern: maintained plateau till the 23rd and then showed steep increase till 36th wg: 125.3±40, 152.6±38 and 158.6±39 in S-PE; 113.5±36, 143.9±43 and 161±29 in PE group (p≤0.05 vs all wg till 23rd, and all wg in NT and CH groups after 23rd gw).

In all groups GFR rose till 32nd wg and slightly decreased in the 36th wg. (p≤0.02: 8th vs. 32nd and 36th wg). GFR in the SPE had the lowest and in CH the highest values during whole pregnancy in comparison to other groups. Both groups without preeclampsia showed non significant decrease of UENa in 18th wg, and than it rose significantly till 32nd wg, more pronounce in NT group (p≤0.007 vs any previous wg).

In 36th wg, hANP correlated inversely with GFR (r =-0.60, p=0.040), UNa/24h (r=- 0.54, p=0.07) and with hematocrit (r=-0.66, p=0.02) in CH and in SPE only with hematocrit (r=-0.42, p=0.02), while in PE positive correlation was found between ANP and hematocrit early in pregnancy – 18thwg, r=0.77, p=0.002.

ANP correlated with MAP24h only in the NT group (r=0.252, p<0.0005). In NT group at 28thwg, by multiple regression analysis (MRA), for MAP24h as dependant variable, p<0.05 was found with body weight and serum uric acid concentrations, and for ANP in 32ndwg, p<0.01 with hematocrit, GFR, MAP24h, BMI.

Figure 1. Changes of hANP in different types of hypertensive disorders of pregnancy



NT-normotensive; CH-chronic hypertension; SPE–preeclampsia superimposed on chronic hypertension, PE-preeclampsia

Discussion

Preeclampsia is a multisystem disorder unique to pregnancy with higher rates in women with preexisting hypertension, diabetes mellitus or previous history of preeclampsia (17). It is considered a disease originated in the activation of the vascular endothelium triggered by placental ischaemia (18-20), and is characterized by generalized vasoconstriction due in part to increased sensitivity of vascular smooth muscles to the effects of vasopressors and by contraction of the plasma volume, which is in contrast to the hypervolemia, high cardiac output and decreased vascular resistance in normal pregnancy (7-9). The increase of hANP secretion is explained by a stretch of left atria resulting from the hypervolemia as a response to variety of stimuli, primarily related to the volume expansion, although other mechanisms may be involved (13, 21-22).

In our study PE and SPE groups demonstrated higher MAP24h, in comparison to the NT and CH groups from the 23rd till 36th wg. (p=0.00001), which is in accordance with the report of Gant 1973 (9) who found that patients determined to develop PE showed attenuation of the refractoriness to pressor agents around the 18th wg, and develop increased sensitivity of vascular smooth muscles to the effects of vasopressors thereafter. It is well established that hANP lowers BP chronically. In our study hANP correlated with MAP24h only in the NT group. The forced MRA model with ANP as a dependent variable was performed and only for ANP in NT group in 32nd wg, p<0.01 was found with hematocrit, GFR, MAP24h, BMI, indicating that ANP is involved in the regulation of BP only during normal pregnancy and that mechanisms that initiate and maintain hypertension during pregnancy are more complex.

In the present study hANP concentrations in NT group were significantly increased in the 36th wg, p<0.001 vs any previous wg. This suggests expanded blood volume or "physiologic hypervolemia" and is in agreement with the results of other studies (13, 22-24). We found that hANP levels in the 8th wg were higher in all hypertensive groups compared to NT, being the highest in SPE. There are reports indicating that high ANP concentrations antedate the clinical manifestation of PE (25). In our previous study (26) we confirmed that PE is associated with early elevation of hANP - in 18th wg gravidas determined to develop PE showed significant sensitivity (69%), specificity (89%) and high positive predictive value (75%) for the cut-off of ≥ 100 pg/ml hANP.

It is well established that ANP concentration are increased in patients with essential and various forms of secondary hypertension (27-29). In our study ANP levels in CH and SPE groups even in early pregnancy were twice to thrice higher compared to levels reported for normotensive pa-

tients, patients with essential, renovascular or renoparenchymal hypertension (28,29). Our results also demonstrated that changes of the concentration of hANP distinguished normotensive and hypertensive pregnancy as well as those with and without preeclampsia, indicating that different mechanisms responsible for the high ANP levels for different types of hypertension in pregnancy.

The renal lesion in PE - glomerular endotheliosis can explain the characteristic decrease in GFR which averages 25% below the rate for normal pregnancy (6). Because GFR normally increases during pregnancy, the values in PE are comparable to those in nonpregnant women (30). In our study, GFR rose till 32nd wg in all groups and decreased in 36th wg. GFR was the lowest in the SPE and the highest in CH group during whole pregnancy compared to other two groups. CH and SPE groups also showed the lowest (CH) and the highest (SPE) hANP level in 32nd wg, pointing to relationship between GFR and ANP levels and vice versa. The reduced GFR that occurred in the SPE may contribute to the reduced clearance of hANP (31). The enhancement of GFR seen by the CH group in comparison to all other groups, may be due to the selective constriction of the glomerular efferent arterioles, a mechanism suggested by the marked increased in filtration fraction produced by hANP, or alternatively, ANP may act on the glomerular membrane, either to oppose Ang II or to directly increase permeability (31).

We found that in 36th wg. hANP in CH group inversely correlated with GFR, UENa and with hematocrit, while in SPE group hANP correlated only with the hematocrit suggesting that in gravidas with CH that did not develop PE, hANP has compensatory and corrective role to the changes in these functions. Preeclampsia is accompanied by amplification of the sodium retention, a feature of normal pregnancy. In the present study, gravidas that did not develop preeclampsia showed non significant decrease of UENa in 18th wg, and significant increase till 32nd wg, more pronounced in NT group, suggesting that in NT sodium retention occurs early in pregnancy and later on hANP regulates UENa and intravascular volume. In our study, SPE group had the highest levels of hANP and it is expected that this should be followed by a highest UENa, which is not the case. This might be result of the lowest GFR presented by this group.

Plasma volume in women with PE is reduced compared with normal pregnancy. In our study a significant positive correlation was found between ANP and hematocrit early in pregnancy (18th wg). Brown 1992 demonstrated that hematocrit is a poor marker of reduced plasma volume in PE (32). In our study the expected normal relation between hANP and hematocrit in CH and SPE groups was present, suggesting that some other factors may interfere with this relation in patients with PE or not all cases with PE have contracted intravascular volume, as demonstrated by Brown 1992. In our study, if we accept hematocrit as a marker of the state of the intravascular volume, both CH and SPE groups showed a physiologic response of ANP.

In PE the redistribution of intravascular volume to interstitial fluid space occurs due to increased capillary permeability (33,34). The high ANP levels in PE may be a result of the elevation in peripheral and renal vascular resistance which along with the increase in the venous tone causes a shift of blood volume towards the cardiopulmonary compartment, with consequent increase in atrial stretch and hANP secretion (33, 34). Significant reduction of GFR that occurs in PE may, also contribute to the reduced clearance of hANP (31).

Our data indicate that PE is associated with elevated plasma hANP that might not be related to hypertension directly. Increments in plasma ANP in the face of plasma volume contraction in SPE and PE appear to be secondary to some other factors (34), which may provide a defence against further vasoconstriction and sodium retention in PE, as we suggested in our previous report (26). In PE, hANP could also play a substantial role in the regulation and/or normalization of the mechanisms which tend to enhance the vasoconstriction in the face of plasma volume contraction (23, 25, 31, 35). It was reported that pregnant women developing preeclampsia lose their usual hemodynamic control and show reactions resembling the nonpregnant state (36). Increased hANP in pregnancy complicated by preeclampsia may result from chronic higher activity of powerfully vasopressor substances and may suggest the decreased ability to compensate and the inability to restore the normal balance between vasodilators and vasoconstrictors or thy lose their usual hemodynamic control (10, 32, 36). This could be a compensatory mechanism to existing marked vasoconstriction and inappropriate sensing of the volume of fluid that fills the vascular bed.

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