Turkish Journal of Endocrinology and Metabolism, (1999) 3 : 143-147 **ORIGINAL ARTICLE**

The Role of Atrial Natriuretic Peptide in Adaptation To Extra-uterine Life and Physiological Weight Loss of the Newborn

Enver Şimşek* **Mehmet Akif Öztürk**** **Ferda Şenel*****

* *Department of Pediatrics, Abant İzzet Baysal University Faculty of Medicine, Bolu, Turkey*
** *Department of Pediatrics, Erciyes University Faculty of Medicine, Bolu, Turkey*
*** *Department of Urology, Abant İzzet Baysal University Faculty of Medicine, Bolu, Turkey*

Atrial natriuretic pe ptide (ANP) is produced primarily in the cardiac atria. Several hormones and neurotransmitters, such as endothelin, arginine-vazopressin, and cathecolamines, directly stimulate the secretion of atrial natriuretic peptide. Increased atrial-wall tension, reflecting increased intravascular volume, is the main stimulus for its release. ANP exerts its effects primarily on the cardiovascular system by reducing the blood pressure and on the kidneys by increasing natriuresis, fractional sodium excretion and fraction of filtration.

To research the role of ANP in weight loss of the newborn in the postnatal first week and in their adaptation to extra-uterine life.

Sixty-one newborns with a mean gestational age of 40 weeks (range 38-42 weeks) were enrolled in the study. We obtained aldosterone and ANP levels from the umbilical artery on the postnatal first day and from the venous blood on the postnatal third and tenth days. Fractional sodium excretion (FENa) was calculated simultaneously.

ANP increased from 12.32 ± 8.94 mmol/L on the postnatal first day to 33.34 ± 17.84 mmol/L on the postnatal third day ($p<0.01$). Aldosterone levels also increased from 98.69 ± 32.07 pg/ml on the postnatal first day to 222.46 ± 102.22 pg/ml on the postnatal third day ($p<0.001$). There was a slight increase in FENa from 0.74 ± 0.66 ion the the postnatal first day to 0.81± 0.54 on the postnatal third day despite a rise in aldosterone concentration. On the postnatal tenth day the levels of ANP and aldosterone decreased to levels similar to those on the postnatal first day. FENa on the tenth day decreased to levels below those on the postnatal first and third days.

The increase in FENa despite the rise in aldosterone levels was attributed to the effect of ANP which might act by inhibiting apical Na^+ channel function or proximal tubular sodium reabsorption. A rise in ANP levels may contribute to weight loss of the newborn during the first five days.

KEY WORDS ANP, weight loss, newborn

Introduction

Atrial natriuretic peptide (ANP) is a 28 amino-acic polypeptide secreted into the blood by atrial myocytes after atrial wall distension (1). All the actions of ANP are mediated by cyclic guanosin monophosphate (cGMP) (2,3). The secretion of stored ANP into the circulation is regulated by the increase of the transmural pressure and atrial

Correspondence address:
Enver ŞİMŞEK
Departmeny of Pediatrics
Abant İzzet Baysal University Faculty of Medicine
Düzce, Bolu
Phone: 0374 541 41 07
Fax: 0374 541 41 05
e-mail: enver@ibu.edu.tr

dilatation (1,4,5). The main effects of ANP are on the cardiovascular and renal systems (Table 1). ANP can produce a variety of physiologic effects including vasodilatation, natriuresis and suppression of the renin-angiotensin-aldosteron axis (2,5,6). ANP reduces peripheral vascular resistance and lowers blood pressure by reducing sympathetic tone (7). The main effect of ANP on renal function is natriuresis by inhibiting angiotensin II stimulated proximal tubules sodium reabsorption, and renin-angiotensin-aldosteron axis (3,8). ANP increases glomerular filtration fraction by increasing the pressure within the glomerular capillaries (9). The net effect of ANP on the renal system is diuresis and natriuresis. During intrauterine life, like many other metabolic functions, the circulation of the fetus depends on the placenta through the umbilical arteries and vein. At the birth fetal circulation must immediately adapt to extrauterine life and the gas exchange is transferred from the placenta to the lungs (10). The removal of the placenta from the circulation also leads to closure of the ductus venosus. The left ventricle is now coupled to the high resistance systemic circulation. The immediately increased pressure causes to increase left atrial wall tension to increase which has a potent stimulatory effect on secretion of ANP from atrial myocytes to the systemic circulation (11). Due to the acute changes in the cardiovascular system renal blood flow and filtration fraction increases rapidly.

Table 1. Site of action and effects of ANP on the circulation (5)

Site of Action	Effect
Capillaries	Plasma volume contraction
Veins	Venodilatation; reduced preload
? Atrial wall	Increased atrial compliance
Arteries	Vasorelaxation, reduced PVR
Vagal afferents	Inhibition of SNA
Renin synthesis	Reduced R-A-A
AngII/endothelin effectors	Hypotension, reduced PVR
Adrenal glomerulosa	Reduced aldosteron secretion
Renal glomerulus and tubule	Natriuresis, leftward shift in pressor-natriuresis curve
Vascular wall	Inhibition of endothelial/VSM cell growth

AngII, Angiotensin; ANP, atrial natriuretic peptide; PVR, peripheral vascular resistance;
R-A-A, renin-angiotensin-aldosterone axis; sympathetic nervous activity; VSM,vascular smooth muscle.

In this study we aimed to search the relation between ANP and aldosteron during the immediately postnatal cardiovascular adaptation.

Materials and Methods

Patients

Sixty-one newborns with a mean gestational age of 40 weeks (range 38-42 week) were enrolled in the study. Seven cases receiving treatment for hyperbilirubinemia and two cases who had neonatal sepsis were excluded from this study. The apgar scores of the cases in the first and fifth minutes after birth were eight and above among neonates included in this study.

Quantitative Analysis

The parameters analyzed in this study were aldosterone and ANP concentrations in the blood samples taken from the umbilical venous blood on the postnatal first day, and venous blood samples obtained on the postnatal third and tenth days. DPC-aldosterone kits were used for aldosterone levels measurement. The RIA method was used in aldosterone assay. Blood samples for ANP were collected in plastic tubes containing aprotinin (Trayslol) 1000 KIU/ml. Blood samples were centrifuged at +4 °C, and the plasma samples were conserved at -20 °C. Samples were prepared according to ANP kit (Amersham) procedure and examined by the RIA method. Simultaneously the fractional sodium excretion on the neonatal first, third and tenth days was also measured.

Body weight measurements

Body weight of the neonates were measured with the same scale by the same person every morning at the same time without clothes.

Statistical analysis

Student's t-test (paired) was used to compare mean ANP, aldosterone, and FENa values. The alpha significance level was accepted as 0,05.

Results

Fractional sodium excretion (FENa)

FENa increased from 0.74± 0.66 in the postnatal first day to 0.81 ± 0.54 on the postnatal third day

(p=NS) and decreased to 0.65 ± 0.53 on the tenth day (p=NS) (Fig 1.).

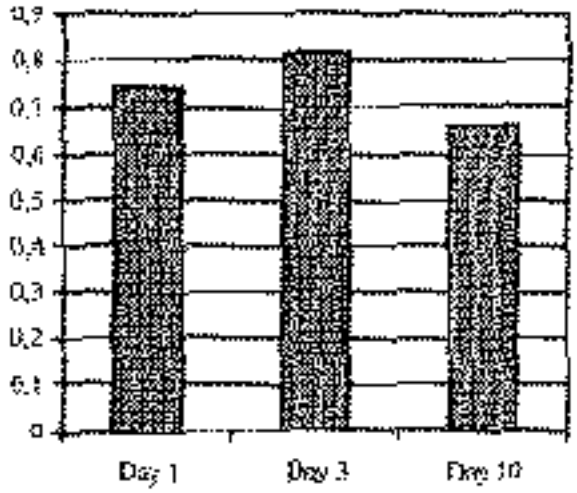

Fig 1. Fractional sodium excretion (FENa) of 61 healty newborns on day 1, 3, and 10 of postnatal life. FENa increased from 0.74 ± 0.66 in the postnatal first day to 0.81 ± 0.54 in the postnatal third day (p=NS) and decreased 0.65 ± 0.53 in the tenth day (p=NS)

Aldosterone

The aldosterone levels increased from 96.69 ± 32.07 pg/ml on the posnatal first day to 222.46 ± 102.22 pg/ml on the posnatal third day (p<0.01). The postnatal third day aldosterone levels decreased to 96.70 ± 65.55 pg/ml on the postnatal tenth day (p< 0.01) (Fig 2).

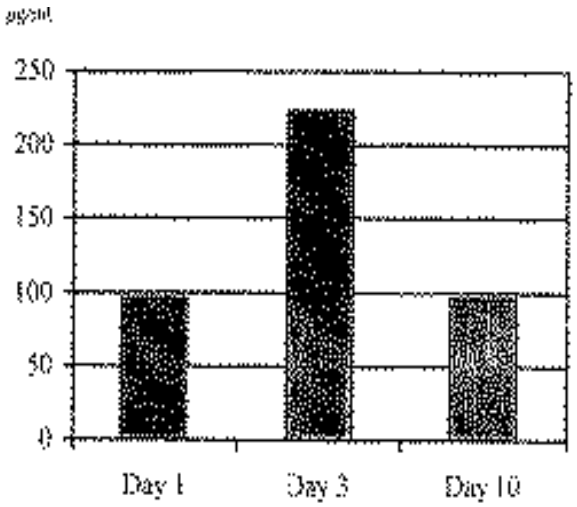

Fig 2. The aldosterone levels of healty newborns on day 1, 3, and 10 of postnatal life. The aldosterone levels increased from 96.69 ± 32.07 pg/ml in the first posnatal day to 222.46 ± 102.22 pg/ml on the third postnatal day (p<0.01). The third postnatal aldosterone levels decreased to 96.70 ± 65.55 pg/ml in the postnatal tenth day (p< 0.01).

The atrial natriuretic peptide

ANP increased from 12.32 ± 8.94 mmol/L on the posnatal first day to 33.34 ± 17.84 mmol/L on the postnatal third day (p<0.01). The postnatal third day ANP decreased to 12.86 ± 8.91 mmol/L on the tenth day (p<0.01) (Fig 3).

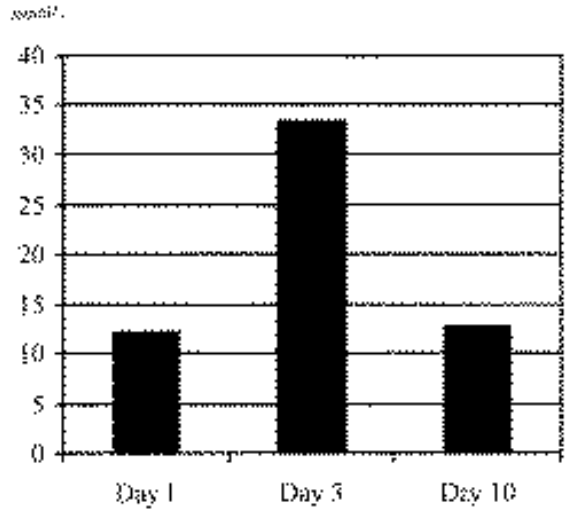

Fig 3. The ANP levels of healty newborns on day 1, 3, and 10 of postnatal life. ANP increased from 12.32 ± 8.94 mmol/L in the first postnatal day to 33.34 ± 17.84 mmol/L in the postnatal third day (p<0.01). The postnatal third day ANP decreased to 12.86 ± 8.91 mmol/L in the tenth day (p<0.01).

Body weight

The weight of the newborns decreased from 3800 ± 245 gram on the postnatal first day to 3750 ± 175 gram on the postnatal third day (p=NS). The weight on the postnatal third day increased to 3835 ± 210 gram (p< 0.05). The difference in fractional sodium excretion on the first, third, and tenth days was not statistically significant.

Discussion

Immediately after clamping the umbilical cord of the newborn during delivery, there are major changes in the physiology of the pulmonary and cardiovascular systems of the newborn as adaptation from fetal to extra-uterine life begins. The most important changes are seen in the cardiovascular system. The myocardial wall-tension acutely increases because of the high systemic arterial pressure. During the fetal life the myocardium contracts against a low systemic pressure, whereas after delivery the systemic

arterial pressure increase immediately due to obliteration of the umbilical blood flow and initiation of respiration. This is the most important stimulus for ANP secretion from cardiac myocytes (1,5). This is the first study that has examined serial FENa, ANP and aldosterone levels simultaneously in healthy mature newborns on day 1, 3 and 10 of postnatal life.

An important factor regulating the renal handling of sodium is the renin-angiotensin system. The renin-angiotensin system regulates tubular sodium reabsorption by direct stimulation of sodium reabsorption in the proximal tubule by angiotensin II and by the stimulation of aldosterone secretion by angiotensin II (14). Aldosterone is an important promoter of sodium reabsorption in the late distal convulated tubule and collecting duct. The target organ of ANP is the kidney, in which it increases sodium and water excretion. In this study there were significant variations in ANP and aldosterone levels throughout the postnatal days 1 to 10. Although aldosterone levels showed a more than two fold increase on postnatal day 3 (from 98.69 ± 32.07 pg/ml on day 1 to 222.46 ± 102.22 pg/ml; $p<0.01$) there was no decrease in FENa. Siegel et al. (12) showed that during the neonatal period fractional sodium excretion reduced with the increasing gestational age, which might be related to an increased response to aldosterone. However, in our study, despite the significant rise in the aldosterone levels during the first 3 days FENa continued to rise although this was not significant. This finding might suggest the existence of another factor that may act on FENa other than aldosterone, as FENa should have been increased with the increased aldosterone levels. Safwate et al (13), in a study performed in new-born calves demonstrated that the renal tubules were able to respond to aldosterone. We also do not think that there is an unresponsiveness to aldosterone at the renal tubular level, but there might be multiple factors which may interfere with the effect of aldosterone by affecting renal tubular sodium reabsorption. There are strong evidences that ANP antagonize the sodium retaining mechanism of the renin-angiotensin system by reducing secretion of aldosterone (1,5). The increased FENa in our study can not be attributed to decreased synthesis of aldosterone as the aldosterone levels rose during the first three days while there was also a rise in ANP levels. ANP causes natriuresis not only by inhibiting aldosteron secretion but also by increasing glomerular fitration fraction (9) and by inhibiting angiotensin II stimulated proximal tubule sodium reabsorption. Thus the increased FENa during the postnatal first three days might be due to the dominant effect of ANP which overcomes the effect of aldosterone. The early postnatal weight loss might also be related to raised ANP levels which causes increased FENa. It was also noted that neonates gained weight simultaneously with the reduction in ANP levels.

This study seems to be the only study examining the relation between ANP, aldosterone, FENa, and weight loss in very early postnatal life where there are major changes in the cardiovascular and pulmonary systems to adjust to the new life. Our results did not show an inhibitory effect of ANP on aldosterone synthesis, at least in the early postnatal life, which is in contradiction with the classical data suggesting reduced synthesis of aldosterone in response to ANP. The role of other factors such as prostaglandins and the kinin system on FENa and early postnatal adaptation remains to be re-searched. Stronger relations between the examined parameters could be achieved by studies enrolling higher patient numbers.

References

1. Levin ER, Gardner DG, Samson WK: Natriuretic peptides. *N Eng J Med* **339:** 321-328, 1998.
2. Inagami T. Atrial natriuretic factor as a volume regulator: *J Clin Pharmacol* **34:** 424-426, 1994.
3. Eitle E, Harris PJ, Morgan TO. Effects of atrial natriuretic factor on cyclic nucleotides in rabbit proximal tubule. *Hypertension* **23:** 358 - 363,1994.
4. Lang RE, Tholken H, Ganten D, Luft FC, Ruskaaho H, Unger T. Atrial natriuretic factor; A circulating hormone stimulated by volume loading. *Nature* **314:** 264-266, 1985.
5. Espiner EA, Richards AM, Yandle TG, Nicholls MG. Natriuretic hormones. *Clin Endocrinol Metab North Am* **24:** 481-509,1995.
6. Harris PJ, Thomas D, Morgan TO. Atrial natriuretic peptide inhibits angiotensin-stimulated proximal tubular sodium and water reabsorption: *Nature* **326:**697-698, 1987.
7. Charles CJ, Espiner EA, Richards AM. Cardiovascular actions of ANF; contributions of renal, neurohumeral,

and hemodynamic factors in sheep: *Am J Physiol* **264:** R533-R538, 1993.

8. Eiskjaer H, Nielsen CB, Sorensen SS, Pederson EB. Renal and hormonal actions of atrial natriuretic peptide during angiotensin II or noradrenalin infusion in man. *Eur J Clin Invest* **26:** 584-585, 1996.
9. Marin-Grez M, Fleming JT, Steinhausen M. Atrial natriuretic peptide causes pre-glomerular vasodilatation and post-glomerular vasoconstriction in rat kidney. *Nature* **324:** 473-476, 1986.
10. Rudolph AM. Distrubition and regulation of blood flow in the fetal and neonatal lamb. *Circ Res* **57:** 811-815, 1985.
11. Teitel D, Iwamoto HS, Rudolph AM. Effects of birth-releated events on central blood flow patterns. *Pediatr Res* **22:** 557-559, 1987.
12. Siegel SR, Oh W. Renal function as a marker of human fetal maturation. *Acta Paediatr Scand* **65:** 481-485, 1976.
13. Safwate A. Urinary sodium excretion and the renin-aldosteron system in new-born calves. *J Physiol* (Lond) **362:** 261-271, 1985.
14. Adelman RD, Solhaug MJ. Patophysiology of body fluids and fluid therapy. In: Nelson Textbook of Pediatrics, 15th edition (Ed: Behrman RE, Kliegman RM, Arvin AM) Philadelphia, WB Saunders, 1996, 185-222.
15. Wijeyaratne CN, Moult PJA. The effect of human atrial natriuretic peptide on plasma volume and vascular permeability in normotensive subjects. *J Clin Endocrinol Metab* **76:** 343-345, 1993.
16. Espiner EA: Physiology of natriuretic peptides. *J Intern Med* **235:** 527-542, 1994.