

The role of serum n-terminal pro-brain natriuretic peptide in transient tachypnea of the newborn

S. KARA, A. TONBUL¹, M. KARABEL², H. AKÇA, N. URAŞ, M. TATLI

Neonatal Intensive Care Clinic, Medical Faculty of Fatih University, ¹Neonatal Clinic of Fatih University, Beştepe, Ankara, Turkey
Pediatric Diseases Hospital, ²Siirt Gynecology and Pediatric Diseases Hospital; Şanlıurfa, Turkey

Abstract. – BACKGROUND AND OBJECTIVES: Transient tachypnea of the newborn (TTN), also known as wet lung disease, is a common cause of respiratory distress in the newborn. It has been demonstrated that, in alveolar type II cell cultures of the rat, receptors affected by the natriuretic peptides are expressed and that atrial natriuretic peptide (ANP) reduced amiloride-sensitive Na⁺ transport in these cells with a pattern similar to that in renal tubules, thereby inhibiting Na⁺ re-absorption in a concentration-dependent manner. Brain natriuretic peptide (BNP) is known to act on these receptors and it is suggested that it may be involved in fluid absorption by the lungs. The present study aimed to investigate the role of BNP in the pathogenesis of transient tachypnea of the newborn.

PATIENTS AND RESULTS: Serum NT-proBNP (N-terminal-proBNP) level measurements of 43 infants diagnosed with transient tachypnea of the newborn were compared to those of 29 healthy neonates. There were no statistically significant differences in NT-proBNP level between the study group and the control group.

CONCLUSIONS: NT-proBNP has no role in the pathophysiology of transient tachypnea of the newborn. Other factors which may potentially be involved in this etiology should be investigated.

Key Words:

Transient tachypnea of the newborn, Natriuretic peptide, N-terminal proBNP, Respiratory distress.

Introduction

Transient tachypnea of the newborn (TTN) is a common cause of respiratory distress during the neonatal period. Although it usually has a benign course and spontaneously resolves over days, TTN may, at times, cause hypoxemia, pulmonary air leaks and persistent hypertension to a degree that necessitates mechanic ventilation^{1,2}.

It has been suggested that TTN may develop due to dysfunction of amiloride-sensitive sodium (Na⁺) channels which are known to have a key role in fetal pulmonary fluid absorption³.

Brain natriuretic peptide (BNP) is known to be synthesized and secreted in response to the circula-

tory load from cardiac ventricular cells, thus being involved in regulation of the bodily water-electrolyte balance and blood pressure. There are studies demonstrating that the levels of Atrial Natriuretic Peptide (ANP), a natriuretic peptide, are decreased in the neonates with respiratory distress.

ANP, natriuretic peptide receptor-A (NPR-A) and NPR-B act over receptors, reduces amiloride-sensitive Na⁺ transport in these cells with this mechanism, thereby inhibiting the Na⁺ re-absorption in a concentration-dependent manner⁶). BNP is also known to have a high affinity to the NPR-A receptor. This may suggest that BNP may have a role in fluid absorption by acting on these receptors in the lungs.

Patients and Methods

This study was conducted at the Neonatal Intensive Care Clinic of Pediatric Health and Diseases Department of the Medical Faculty of Fatih University between January 2009 and February 2010. A total of 43 infants, 23 males and 20 females, with gestational ages of 32-39 weeks, who were being monitored on an inpatient basis for transient tachypnea of the newborn, constituted the study group. The control group included 29 healthy infants, 21 males and 8 females, with gestational ages of 31-39 weeks. In this prospective study, the diagnosis of transient tachypnea of the newborn was established according to the following criteria:

1. Tachypnea (respiratory rate > 60/min) which develops during the first 6 hours following delivery;
2. Tachypnea which persists for at least 12 hours;
3. Presence of findings consistent with transient tachypnea of the newborn in chest radiography (e.g., hyperaeration, mild cardiomegaly, distinction of pulmonary vascular structures, pleural or interstitial fluid);
4. Absence of hyaline membrane disease, meconium aspiration syndrome, congenital pulmonary abnormalities and congenital heart disease⁷.

Infants with the conditions listed above who were not delivered at intensive care unit (ICU) but were referred from other healthcare facilities after the first 6 hours of life, those who were administered furosemide treatment during their clinical monitoring, those with proliferation in blood culture, those with increased levels of C-reactive protein (CRP) and interleukin-6 (IL-6) or immature/total neutrophil and treated for sepsis were excluded from the study. Infants being monitored for transient tachypnea of the newborn were placed under supervision at the neonatal intensive care unit (NICU) and their body weight, height and head circumference were measured and venous blood gas measurement were taken after which oxygen treatment was started. The infants were monitored for the oxygen therapy and other medication they received, for vital findings such as respiratory rate, heart rate and blood pressure and for oxygen saturation. During the first four post-natal hours, the infants were also monitored for whole blood count, CRP and IL-6 values. During the postnatal 0-24 hours, blood samples were collected in 2-ml vials for NT-proBNP (N-terminal-proBNP) assays and sera were separated by centrifuging at 4000 rpm for 6 minutes and the obtained samples were stored in Eppendorf vials at -80°C . For infants being monitored for transient tachypnea of the newborn, lung radiographies were taken and other conditions which might have caused tachypnea were ruled out. Each infant underwent echocardiographic analyses during the first 48 hours and presence of patent ductus arteriosus (PDA) was investigated. All mothers were questioned for any current medications, presence of asthma, level of education, diabetes, smoking and infection history. Serum NT-proBNP measurements were taken using USCN Life Science (Wuhan, P.R. China) brand ELISA kits.

Statistical Analysis

Analyses on the data were performed using the SPSS for Windows v11.5 software package (SPSS Inc., Chicago, IL, USA). Shapiro Wilk test was used to determine whether the distribution of continuous variables was close to normal. Descriptive statistics for continuous variables were demonstrated as mean \pm standard deviation and medians (minimum-maximum). Nominal variables were expressed as number of infants and percentages. Significance of differences between intergroup mean values was studied using Student's *t* test while significance for medians were assessed using Mann-Whitney U test. Nominal variables were studied using Pearson's chi-square or Fisher's exact chi-square test. Statistical significance was set at $p < 0.05$.

Results

Demographic data of respective groups are listed in Table I. There was a statistically significant difference in average maternal age between the study and control groups, the mothers of the infants in the study group being older than those compared to the control group ($p = 0.029$). The two groups did not differ significantly in number of pregnancies ($p = 0.087$). Average number of births was statistically significantly higher in the control group than the study group ($p = 0.028$). The groups did not differ significantly in the number of abortion/stillbirth ($p = 0.296$). Average gestational weeks were similar between the groups ($p = 0.961$). Level of education was not significantly different between the groups ($p = 0.223$).

Distribution of the infants in terms of the mode of delivery were statistically similar between the two groups ($p = 0.271$). While none of the infants in the control group had early membrane rupture (EMR), 7% of the infants had positive EMR although the rates of EMR positivity were statistically similar between the groups ($p = 0.268$). The study and control groups did not differ statistically significantly in gender distribution of the infants ($p = 0.106$). There was a statically significant difference between the two groups in birth weight: average birth weight of the infants in the study group was lower than that of the control group ($p = 0.034$). The two groups also differed significantly in 1- and 5-minute Apgar scores, with both values being lower in the study group compared to the control group ($p < 0.001$ and $p < 0.001$, respectively).

None of the subjects in the control group had history of medicine or steroid treatment, while 9.3 and 14 % of those in the study group had history of drug or steroid treatment, respectively. The two groups, however, did not differ significantly in previous drug or steroid use ($p = 0.143$ and $p = 0.075$, respectively).

It was not possible to make a statistical comparison between the two groups in terms of clinical characteristics because all clinical features were constant in the control group (i.e., there exists no statistically significant difference in any feature, except for respiratory rate and duration of hospital stay [$p < 0.001$]) (Table II).

Of the subjects in the study group, 9.3% had pneumothorax and 7% had pneumonia while none of the subjects in the control group had any of these two conditions. The distribution of subjects in the two groups in terms of pneumothorax and pneumonia, however, were statistically similar ($p = 0.143$ and $p = 0.268$).

Table I. Demographic characteristics of subjects by group.

| Variable | Study group (n = 43) | Control group(n = 29) | p |
|-------------------------|----------------------|-----------------------|---------|
| Maternal age (years) | 29.6 ± 4.5 | 27.2 ± 3.8 | 0.029 |
| Parity | 2.2 ± 0.9 | 1.8 ± 0.8 | 0.028 |
| Abortion/stillbirth (%) | 12 (27.9%) | 5 (17.2%) | 0.296 |
| Mother' education | | | 0.223 |
| Primary | 12 (41.1%) | 6 (20.7%) | |
| Secondary | 11 (37.9%) | 16 (55.2%) | |
| University | 6 (20.7%) | 7 (24.1%) | |
| Mode of delivery | | | 0.271 |
| Normal vaginal | 6 (14.0%) | 7 (24.1%) | |
| C/S | 37 (86.0%) | 22 (75.9%) | |
| EMR | 3 (7.0%) | – | 0.268 |
| Infant gender | | | 0.106 |
| Female | 20 (46.5%) | 8 (27.6%) | |
| Male | 23 (53.5%) | 21 (72.4%) | |
| Gestational week | 35.7 ± 1.7 | 35.7 ± 0.8 | 0.961 |
| Birth weight (g) | 2691 ± 594 | 2924 ± 317 | 0.034 |
| Apgar 1 min | 7 (4-9) | 8 (7-9) | < 0.001 |
| Apgar 5 min | 9 (7-10) | 10 (9-10) | < 0.001 |

*The study group assessments are based on 29 subjects.

The comparison of the infants with transient tachypnea of the newborn and healthy neonates in terms of the laboratory results demonstrated no differences in hemoglobin, hematocrit, leukocytes, platelets, CRP and IL-6 measurements. Echocardiographic analyses performed for all subjects of the study showed that the infants in both groups were similar in terms of patent ductus arteriosus (PDA) presence: PDA was not identified in any of the infants in either group.

The average serum NT-proBNP level was 6.7 ng/ml (1.3-21.0) in the study group versus 7.5 ng/ml (2.7-21.0) in the control group. The study and control groups did not differ statistically significantly in average pro-BNP levels ($p = 0.491$).

No statistically significant correlation was noted between gestational age and pro-BNP ($r = 0.105$ and $p = 0.380$). Average level of pro-BNP in subjects with normal vaginal delivery (NVD) is 5.9 ng/ml (1.8-21.0) compared to 7.93 ng/ml (1.8-21.0) in those who delivered with cesarean section (C/S),

Table II. Distribution of subjects in the study group by clinical findings.

| Variable | Study group (n = 43) |
|-----------------------|----------------------|
| Retraction | 41 (95.3%) |
| Tachypnea | 41 (95.3%) |
| Moaning | 37 (86.0%) |
| Cyanosis | 11 (25.6%) |
| Length of stay (days) | 5 (1-18) |

with no statistically significant changes in pro-BNP levels by the mode of delivery ($p = 0.655$).

Median levels of NT-proBNP in the two groups by gender were 6.8 (1.6-21.0) for females and 7.0 (1.3-21.0) for males: NT-proBNP levels did not vary significantly by gender ($p = 0.903$).

Discussion

As a common cause of respiratory distress in the neonatal period, transient tachypnea of the newborn is often a self-limited condition with a benign course^{1,2,8}.

Pathophysiology of transient tachypnea of the newborn has not been fully elucidated to date. Delayed absorption of fetal lung fluid which leads to pulmonary edema is involved in the process². It is suggested that, in prematurely delivered infants or in those who are delivered via cesarean section before the onset of labor, there is not enough time for elimination of fetal lung fluid and that the excess fluid in the lungs of such infants at delivery passes from the alveoli to interstitium to accumulate in perivascular tissues resulting in airway obstruction associated with the distress induced on small airways and, consequently, in hyperaeration⁹. In studies which aimed at investigating the risk factors involved in development of transient tachypnea of the newborn, it has been demonstrated that the gestation period and the dose and time of narcotic analgesics administered to the mother during labor were not risk factors for transient tachypnea of the new-

born. These studies also showed that infants of male gender were more common in the transient tachypnea of the newborn group, that macrosomia was more frequent among infants with transient tachypnea of the newborn although percentage of maternal diabetes was not higher, and that the interval between membrane rupture and delivery was longer^{10,11}. In the present study, the two groups did not differ significantly in gestation period. Male gender has been shown to be a risk factor in transient tachypnea of the newborn in several studies⁷. In the present study, however, the control and study groups did not differ statistically significantly in infants' gender distribution ($p = 0.106$). Unlike the previous studies, our study group had a lower birth weight than that of the control group. This could be explained by the limited number of subjects.

Elective cesarean section before the onset of labor is the most well-known risk factor for transient tachypnea of the newborn¹¹. However, the fact that the majority of the infants delivered via cesarean section did not have transient tachypnea with the condition being observed only in a few of them indicates that multiple factors, which are currently unexplained, are involved in the pathophysiology of the condition. A study has demonstrated a 19-fold increased prevalence of BNP in infants delivered via normal vaginal delivery compared to elective cesarean section, which had been associated with the stress spontaneous delivery causes on the infant¹². Since the present study aimed to investigate the role of serum NT-proBNP levels in the pathophysiology of transient tachypnea of the newborn and with a view to minimizing the potential bias of modes of delivery on serum NT-proBNP levels, infants delivered via both normal spontaneous birth and cesarean section were included so that the two groups did not differ in mode of delivery.

Proposed accounts of the pathophysiology of transient tachypnea of the newborn also focus the role of maternal bronchial asthma. There are reports indicating that maternal asthma was a risk factor for transient tachypnea of the newborn, not only for premature infants but particularly pronounced among term ones. Although the exact mechanism is not known, it has been suggested that β -adrenergic unresponsiveness may be involved in the occurrence of transient tachypnea of the newborn in term infants. It is, therefore, likely that maternal asthma, which may be associated with β -adrenergic unresponsiveness, is a risk factor for transient tachypnea of the newborn in term infants¹³. None of the infants in the present study had history of maternal asthma.

It has been reported that the extent of weight loss

following delivery was less in transient tachypnea of the newborn and this was associated with retention of the lung fluid. Based on this, the role of diuretics in transient tachypnea of the newborn was investigated but no differences were noted in the clinical course of the infants with transient tachypnea of the newborn treated with furosemide¹⁴. This leads to the assumption that other mechanisms, in addition to excess total fluid, were also involved in the process. Infants treated with furosemide were excluded from the present study to avoid confounding.

As described previously, amiloride-sensitive Na^+ channels have the major role in clearance of the excess fluid during the fetal period, but the evidence on how and when these start functioning is lacking. It is, however, certain that the more fluid is absorbed during the prenatal period, the more advantageous the neonate will be since during the first inhalation, efficacy of pulmonary gas exchange will increase in proportion to amount of fluid in the lungs – the less fluid the higher efficacy. Currently, the rate at which this pulmonary fluid is eliminated during prenatal and postnatal periods is not exactly known. While there are investigations which demonstrate that fetal lung fluid is eliminated five days prior to delivery, contradicting reports also exist. The only mechanism known to reduce the levels of fluid in the lungs during labor is reabsorption of sodium from the lumen. This mechanism is activated through increased levels of epinephrine during delivery and, based on experiments, the amount of fluid removable by this mechanism was calculated approximately as 20 ml, in which case there would remain a higher amount of fluid. A study by Berger et al¹⁵ demonstrated that more than 75% of fetal lung fluid is eliminated before normal term delivery and this explains why elective cesarean section is associated with an increased risk of transient tachypnea of the newborn.

The mechanisms by which lung fluid is absorbed during the perinatal period has not been fully understood. Epinephrine induces β_2 activation of the Na^+ pumps in the pulmonary epithelium, leading to transition of the lungs from secretory to absorptive phase. Maturation of this mechanism is controlled by cortisol and thyroid hormones and development of transient tachypnea of the newborn has been shown in infants in whom this pump is not activated. Another circulatory agent that initiates sodium absorption is arginine vasopressin but it is known that this agent is not sufficiently effective alone. Thus, although the role of amiloride-sensitive sodium channels in elimination of fetal lung fluid has been indisputably demonstrated by several experi-

mental researches, how the functioning of these ECNa channels are regulated and from which factors it is affected is not precisely known^{15,16}.

Inadequate prenatal absorption of the fetal lung fluid associated with elective cesarean section may be involved in transient tachypnea of the newborn. A disorder of ion transport in pulmonary epithelium may be another causative factor. As a matter of fact, a study by Gowen et al¹⁷ investigated electrical potential differences (PD), an indicator of ion transport from nasal epithelium, and found higher baseline PD values for infants with transient tachypnea of the newborn compared to other subjects. These higher levels in infants with transient tachypnea of the newborn returned to normal after 72 hours and this was simultaneous with and corresponded to the normalization of infants' respiratory rates. Based on these evidences, it may be suggested that the delay in transition of the pulmonary epithelium from Cl⁻ secretion to Na⁺ absorption is one of the components in the pathophysiology of transient tachypnea of the newborn. Whether labor started is not influential on PD outcomes but this alone does not suffice to explain the PD differences in transient tachypnea of the newborn. Although the study by Gowen et al¹⁷ does not explain the reason underlying the dysfunction of epithelial ion transport in transient tachypnea of the newborn, it does support that the process of labor has a key role in pulmonary ion transport at delivery in neonates. The most remarkable aspects of the dysfunction of epithelial ion transport, which has been experimentally demonstrated to be present in transient tachypnea of the newborn, are that the condition is transient and it resolves spontaneously in 72 hours.

NT-proBNP is another factor that may have an effect on epithelial ion transport in the lungs. The studies on ANP, a natriuretic peptide, in the neonatal period focused rather on its effect on fluid and electrolyte balance. Two studies investigated the alternations in body weight and blood pressure relative to ANP and aldosterone levels in healthy term and premature infants: a significant correlation was reported between ANP concentrations and the degree of weight loss in the infants on day 4 and the Authors suggested that ANP and aldosterone regulated the vascular volume during the period of adaptation of the neonates to postnatal life^{18,19}. The potential link between ANP and this dysfunction in ion transport, which has been demonstrated previously to be involved in the pathophysiology of the transient tachypnea of the newborn, was studied but no significant differences were noted between the

two groups in serum pro-ANP levels measured both on the first and the third days²⁰. In 1998, it has been shown that both natriuretic peptide receptor-A (NPR-A) and NPR-B are expressed in mice alveolar type II cell cultures, that ANP reduced amiloride-sensitive Na⁺ transport in these cells as in renal tubules, thus inhibiting Na⁺ reabsorption in a concentration-dependent manner⁶. BNP is known to have a high affinity to NPR-A receptor. It may, therefore, be concluded that BNP may have a role similar to that of ANP in the lungs. On the other hand, preventive effect of BNP has been shown in bronchoconstriction-induced animal models with microvascular leak²¹. A linear relationship has been defined between the severity of respiratory distress syndrome (RDS) and NT-proBNP in premature neonates. This study started with 45 infants. In these infants with gestational weeks of 25-33, RDS was noted in a total of 21 infants; mild in 7, moderate in 10 and severe in 4. Infants with severe RDS had significantly higher levels of NT-proBNP compared to the other two groups. Based on this finding, the Authors emphasized that BNP had a key role in pulmonary hemodynamic variations²². There are several reports which demonstrate changes in serum BNP measurements not only in cardiac diseases but also in other conditions associated with the lungs²³⁻²⁵. A work by Reel et al²⁵ in 45 patients diagnosed with "acute lung damage – acute respiratory distress syndrome" (21 cases of pneumonia, 4 cases of aspiration, 6 cases of lung trauma, 4 cases with heart disease, 3 cases of sepsis and 10 other) monitored serum BNP levels over the first 24 hours following diagnosis. The Authors found statistically significant increases in BNP levels with worse clinic course in those with very high levels of BNP. Based on these findings, it was suggested that BNP may be used for the prognosis of lung diseases. It is known that clearance of excess fluid from lungs is delayed in transient tachypnea of the newborn. Natriuretic peptides are acknowledged to induce diuresis and natriuresis, with activity triggered in hypervolemia. Their involvement in hemodynamic changes in the lungs has been shown recently^{23,24}.

Conclusions

The present study has been planned based on the hypothesis that BNP is released in insufficient levels in transient tachypnea of the newborn and, therefore, lung fluid is not eliminated adequately. Although it was expected with this work to observe lower levels of serum NT-proBNP in infants diag-

nosed with transient tachypnea of the newborn compared to those in the control group, no statistical differences were observed between the patient and control groups in terms of NT-proBNP levels. While this may indicate that NT-proBNP has no role in the pathophysiology of the transient tachypnea of the newborn, a link with the fact that serum NT-proBNP levels are affected from multiple factors and that there are variations in the number and responsiveness of receptors is also likely. We believe that further studies at different levels with larger series of subjects are needed.

Conflict of Interest

None declared.

References

- 1) TUTDIBI E, GRIES K, BÜCHELER M, MISSELWITZ B, SCHLOSSER RL, GORTNER L. Impact of labor on outcomes in transient tachypnea of the newborn: population-based study. *Pediatrics* 2010; 125: 577-583.
- 2) HANSEN T, CORBET A. Disorders of the transition: Avery's diseases of the newborn. 8. ed. Taeusch HW, Ballard RA (eds) W.B. Saunders Co, Philadelphia, 2004, S: 333-334.
- 3) HUMMLER E, BARKER P, BEERMANN F. Role of the epithelial sodium channel in lung liquid clearance. *Chest* 1997; 111: 113.
- 4) ESPINER EA, RICHARDS AM, YANDLE TG, NICHOLLS MG. Natriuretic hormones. *Endocrin Metab Clin North Am* 1995; 24: 481-509.
- 5) THARAUX PL, DUSSAULE JC, COUETTE S, CLERICI C. Evidence for functional ANP receptors in cultured alveolar type II cells. *Am J Physiol* 1998; 274: 244-251.
- 6) ITO Y, MARUMO F, ANDO K, HAYASHI M, YAMASHITA F. The physiological and biological significances of human atrial natriuretic peptide in neonates. *Acta Paediatr Scand* 1990; 79: 26-31.
- 7) DANI C, REALI MF, BERTINI G, WIECHMANN L, SPAGNOLO A, TANGUCCI M, RUBALTELLI FF AND THE ITALIAN GROUP OF NEONATAL PNEUMOLOGY. Risk factors for the development of respiratory distress syndrome and transient tachypnea in newborn infants. *Eur Respir J* 1999; 14: 155-159.
- 8) RAWLINGS JS, WILSON JL. Radiological case of the month: transient tachypnea of the newborn. *Am J Dis Child* 1985; 139: 1233-1234.
- 9) TUTDIBI E, HOSPES B, LANDMANN E, GORTNER L, SATAR M, YURDAKOK M, DELLAGRAMMATICAS H, ORS R, ILIKKAN B, OVALI F, SARMAN G, KUMRAL A, ARSLANOGLU S, KOC H, YILDIRAN A. Transient tachypnea of the newborn (TTN): a role for polymorphisms of surfactant protein B (SP-B) encoding gene? *Klin Padiatr* 2003; 215: 248-252.
- 10) RISKI A, ABEND WEINGER M, RISKIN-MASHIAH S, KUGELMAN A, BADER D. Cesarean section, gestational age, and transient tachypnea of the newborn: timing is the key. *Am J Perinatol* 2005; 22: 377-382.
- 11) RAWLINGS JS, SMITH FR. Transient tachypnea of the newborn. An analysis of neonatal and obstetric risk factors. *Am J Dis Child* 1984; 138: 869-871.
- 12) ITOH H, SAGAWA N, HASEGAWA M, OKAGAKI A, INAMORI K, IHARA Y, MORI T, SUGA S, MUKOYAMA M, SHIRAKAMI G, ET AL. Brain natriuretic peptide levels in the umbilical venous plasma are elevated in fetal distress. *Biol Neonate* 1993; 64: 18-25.
- 13) DEMISSIE K, MARCELLA SW, BRECKENRIDGE MB, RHOADS GG. Maternal asthma and transient tachypnea of the newborn. *Pediatrics* 1998; 102: 84-90.
- 14) WISWELL TE, RAWLINGS JS, SMITH FR, GOO ED. Effect of furosemide on the clinical course of transient tachypnea of the newborn. *Pediatrics* 1985; 75: 908-910.
- 15) BERGER PJ, KYRIAKIDES MA, SMOLICH JJ. Massive decline in lung liquid before vaginal delivery at term in the fetal lamb. *Am J Obstet Gynecol* 1998; 178: 223-227.
- 16) HUMMLER E, BARKER P, GATZY J, BEERMANN F, VERDUMO C, SCHMIDT A, BOUCHER R, ROSSIER BC. Early death due to defective neonatal lung liquid clearance in alphaENaC-deficient mice. *Nat Genet* 1996; 12: 325-328.
- 17) GOWEN CW, LAWSON EE, GINGRAS J, BOUCHER RC, GATZY JT, KNOWLES MR. Electrical potential difference and ion transport across nasal epithelium of term neonates: Correlation with mode of delivery, transient tachypnea of newborn, and respiratory rate. *J Pediatr* 1988; 113: 121-127.
- 18) GEMELLI M, MAMI C, DE LUCA F, STELITANO L, BONACCORSI P, MARTINO F. Atrial natriuretic peptide and renin-aldosterone relationship in healthy newborn infants. *Acta Paediatr Scand* 1991; 80: 1128-1133.
- 19) PAC FA, YIGITOGU MR, KALAYCI AG, ADAM B. Atrial natriuretic peptide and aldosterone in sick premature neonates. *Turk J Pediatr* 1992; 34: 153-156.
- 20) ÖNAL EE, DILMEN U, ADAM B, TÜRKYLMAZ C, KİTAPÇI F, OUZ D. Serum atrial natriuretic peptide levels in infants with transient tachypnea of the newborn. *J Matern Fetal Neonatal Med* 2005; 17: 145-149.
- 21) TAKAGI K, ARAKI N. Relaxant effects of brain natriuretic peptide on guinea-pig tracheal smooth muscle. *Clin Exp Pharmacol Physiol* 1993; 20: 239-243.
- 22) ROCHA G, CLEMENTE F, RODRIGUES T, GUIMARÃES H. Clinical significance of plasma n-terminal pro-b-type natriuretic peptide in respiratory distress syndrome of the preterm neonate. *Acta Med Port* 2009; 22: 349-354.
- 23) LIN Y, HAO J, YAO GQ, ZHAO JJ, ZHU X. Prognostic value of assay of brain natriuretic peptide in patients with acute respiratory distress syndrome. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue* 2010; 22: 285-287.
- 24) LEUCHTE HH, BAUMGARTNER RA, NOUNOU ME, VOGESER M, NEUROHR C, TRAUTNITZ M, BEHR J. Brain natriuretic peptide is a prognostic parameter in chronic lung disease. *Am J Respir Crit Care Med* 2006; 173: 744-750.
- 25) REEL B, OISHI PE, HSU JH, GILDENGORIN G, MATTHAY MA, FINEMAN JR, FLORI H. Early elevations in B-type natriuretic peptide levels are associated with poor clinical outcomes in pediatric acute lung injury. *Pediatr Pulmonol* 2009; 44: 1118-1124.