INCREASED ASYMMETRIC DIMETHYLARGININ LEVELS IN SEVERE TRANSIENT TACHYPNEA OF THE NEWBORN

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Transient tachypnea of the newborn (TTN)

- The most common cause of neonatal respiratory distress .
- The incidence; 1-2 % in all infants
- Inadequate or delayed neonatal lung fluid clearance
- The lung fluid clearance begins antenatally at late gestation and accelerates with the onset of labor by the effect of hormonal changes

Transient tachypnea of the newborn (TTN)

- The lung fluid usually completely absorbed by 48 to 72 hours
- Hypoxemia, pulmonary hypertension, pulmonary air leakage syndromes and prolonged intensive care.

ASYMMETRIC DIMETHYLARGININ (ADMA)

- Nitric oxide (NO);

  - synthesized from arginine by the NO-synthese in the lung

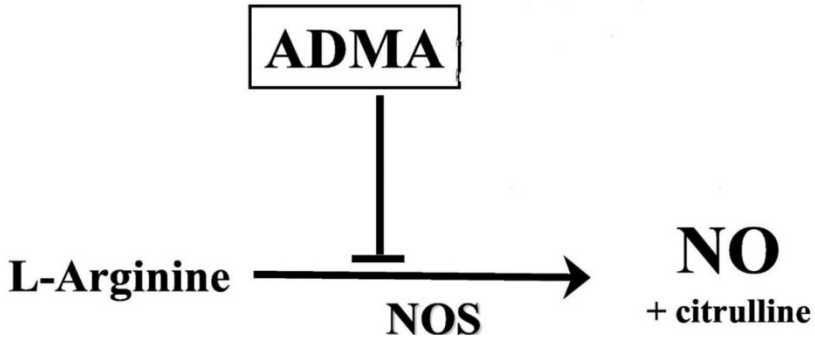
  - an important mediator in normal lung development, vascular smooth muscle relaxation, ventilation perfusion matching and physiologic pulmonary vasodilation.

- NO has been suggested to play a key role in the pathogenesis of pulmonary hypertension

ASYMMETRIC DIMETHYLARGININ (ADMA)

- Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of NO synthese shown to contribute regulation of vascular tone

- Increased ADMA levels have been found in vessel diseases and pulmonary hypertension in patients with congenital heart disease



Aim

- To investigate serum ADMA levels in infants with TTN and its relation to pulmonary artery systolic pressure (PASP) and disease severity

Methods

- A prospective controlled study
- Term and late-preterm (≥34 weeks) infants were enrolled

Methods

- **If they fulfill the following criteria diagnosed as TTN;**

  (1) onset of respiratory distress (tachypnea, retractions, grunting, nasal flaring, mild cyanosis) within 6 h after birth

  (2) persistence of respiratory distress beyond 12 h after birth

  (3) chest X-ray consistent with TTN (perihilar streaking, hyperinflated lungs, flattening of the diaphragm, and fluid in the fissures)

Methods

- **Exclusion criteria**: Maternal diabetes, preeclampsia, prolonged rupture of membranes (> 18 hours), other causes of tachypnea (respiratory distress syndrome, pneumonia, meconium aspiration, polycythemia, hypoglycemia, early onset sepsis, congenital heart disease, hemodynamically significant patent ductus arteriosus), congenital anomalies and birth asphyxia.

Methods

- Venous blood (2 cc) from a peripheral vein were obtained in study and control groups at 6-24th (first samples) and 48-72th hours (second samples) of life for ADMA.
- Samples were stored at -80° C until analysis.
- Serum ADMA levels were measured by ELISA method (Immun Diagnostics, Germany).

Methods

- Patients were divided into 2 groups according to duration of tacypnea

  prolonged (>72 hours) and

  mild tachypnea (≤ 72 hours)

Methods

- Pulmonary artery systolic pressure (PASP) were evaluated by echocardiography in the study group on the second day of life.
- PASP was estimated by Doppler echocardiography from the systolic right ventricular to right atrial pressure gradient using the modified Bernoulli equation (4 x peak tricuspid regurgitant velocity^2)
- Pulmonary hypertension was considered as values above 36 mmHg in the study group.

Methods

- Statistical analyses were conducted using the SPSS version 17.0 (SPSS Inc., Chicago, IL)
- Student *t* test and Mann- Whitney test were used to compare continuous parametric and nonparametric variables.
- The chi-square ($\chi 2$) test was used to compare categorical variables.
- Pearson's correlation coefficent was used to test the relationship between serum ADMA levels and tachypnea duration.
- Data are expressed as mean $\pm$ standart deviation, or as percentages.
- p value was considered significant if <0.05

Results

- Thirty- eight infants with TTN and 41 controls were enrolled.
- Demographic characteristics of the study and control groups were similar.

Demographic characteristics:

	Patients (n=38)	Controls (n=41)	p
Birth weight(gr)	2740±354	2906±548	0.192
Gestational age (week)	36 (34-40)	36.8 (34-41)	0.062
Sex (Female/Male)	14/24	21/20	0.176
Cesarean section, n (%)	27(71%)	19 (46%)	0.039
Maternal age(years)	27.6 (50-190)	120 (48-210)	0.039
Apgar (5 minute)	9 (7-10)	9 (8-10)	0.185
- Supplemantal oxygen - Nasal CPAP - Intubation	16 (42.1 %) 20 (52.6 %) 2 (5.3 %)		
PASP (mmHg)	27.3 ±9.7		
Complications pneumothorax pulmonary hypertension	1 (1.6 %) 6 (15.8 %)		

Patients and controls ADMA levels;

	Patients (n=38)	Controls (n=41)	p
ADMA first day (first sample)	1.06 ±0.26	0.83 ±0.18	**0.001**
ADMA third day (second sample)	0.85 ±0.17	0.81 ±0.1	0.302

- In the first samples ADMA levels were significantly higher in patients with TTN compared to controls (p=0.001)

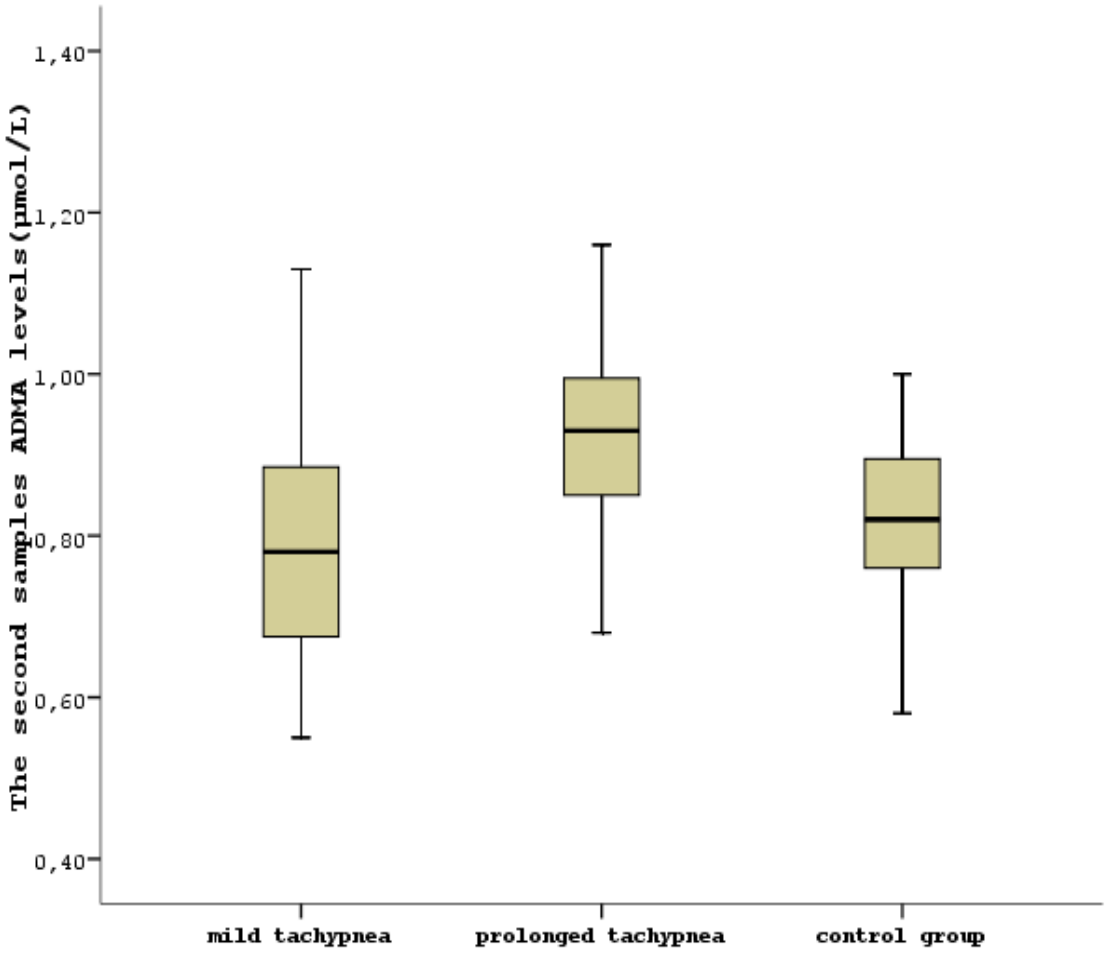
Relation of ADMA levels and duration of tachypnea

	Mild tachypnea <72 h (n=19)	Prolonged tachypnea >72 h (n=19)	p
BW (gr)	2691±316	2781±392	0.405
GA (week)	36.1(34-41)	36 (34-40)	0.643
Sex (F/M)	8/11	6/13	0.737
Cesarean section, n (%)	11 (57,8%)	16 (84,2%)	0.139
Duration of tachypnea (hours, min–max)	65 (24-72)	96 (75-168)	**<0.001**
Ratio of mechanical ventilation (n,%)	9 (50%)	13 (68%)	0.325
ADMA first samples (mean ±SD)	1.07±0.16	1.04±0.32	0.425
ADMA second samples (mean ±SD)	0.79±0.15	0.91 ±0.18	**0.025**
PASP (mmHg)	23.6±7.4	30.8±10.5	**0.042**

Relation of ADMA levels and duration of tachypnea

In the second samples ADMA levels were significantly higher in infants with prolonged tachypnea compared with to mild tachypnea (p=0.025) and controls (p=0.014).

Second samples' ADMA levels were correlated with tachypnea duration (p=0.033; r= 0.346).



Discussion

- **ADMA**; inhibits endothelial NO synthese, that inhibition decreases NO production in the vascular endothelium.
- Elevated ADMA levels may cause endothelial dysfunction.

•Golikorsky MS. Endothelial cell dysfuntion: can't live with it, how to live without it. Am J Physiol 2005; 288: F871-80

- To date, elevated ADMA levels have been detected in numerous diseases incluiding hypertension, atherosclerosis, diabetes mellitus, renal insufficiency, hypercholesterolemi and hyperhomocysteinemia.

•Cooke JP. ADMA: its role in vascular disease. Vasc Med 2005;10: S11-7.
•Leiper JM, Vallance P. The synthesis and metabolism of asymmetric dimethylarginine (ADMA). Eur J Clin Pharmacol 2006;62:33-8.
• Zoccali C, Kielstein JT. Asymmetric dimethylarginine: a new player in the pathogenesis of renal disease? Curr Opin Nephrol Hypertens 2006; 15:314-20.
•Slaghekke F, Dekker G, Jeffries B. Endogenous inhibitors of nitricoxide and preeclampsia: a review. J Matern Fetal Neonatal Med 2006; 19:447-52.

- An elevated circulating consentration ADMA was reported that might contributed to pulmonary hypertension in patients with congenital heart diseases.

- Increased pulmonary concentrations of ADMA was demonstrated in the rat model with chronic hypoxia- induced pulmonary hypertension.

•Gorenflo M,Zheng C, Werle E, et al. Plasma levels of assymetricdimethyl L-arginine in patients with congenital heart disease and pulmonary hypertension.J Cardiovasc Pharmacol.2001;37:489-92
•Milatt et al. Evidence of dysregulation of dimethyl arginine dimethylaminohydrolase I in Chronic Hypoxia-Induced Pulmonary Hypertension. Circulation.2003;108:1493-98

- It was reported that high plasma ADMA concentrations could be associated with decrased NO synthesis, which seems to be important for the development of the lungs and could possibly lead to an increased period of mechanical ventilation in preterm infants.

•Richir M.C. Plasma ADMA concentrations at Birth and Mechanical Ventilation in Preterm Infants.: A prospective Pilot Study.Pediatric Pulmonology 2008 43: 1161-66

TTN and echocardiography signs;

- In a study evaluating cardiac functions reported that patients with severe TTN had more myocardial failure and pulmonary hypertension than benign TTN.

Halliday H. McClure G. Reid M. Transient tachypnea of the newborn: two distinct clinical entities Arc Dis in Childhood 1981, 56, 322-25

- Systolic functions were found near to lower limit of normal but significantly lower in patients with TTN which may indicate forced or delayed cardiovascular adaptation to extrauterine life.

Aydemir O. et al. The role of plasma N-terminal pro-B-type natriuretic peptide in predicting the severity of transient tachypnea of the newborn. Early human development, 2012, 88.5: 315-319.

What this study adds?

- In the present study, we measured serum ADMA levels for the first time in newborns with TTN and investigated the relationship between PASP and severity of disease.

- We demonstrated higher ADMA levels and PASP in infants with prolonged tachypnea.

Conclusion

An increased ADMA concentration may reduce NO synthesis, which leads to increased pulmonary artery pressure and consequently a longer duration of tachypnea.